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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ARMOUR, Duncan, Robert [GB/GB]; Discovery Chemistry, IPC 924, Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). BROWN, David [GB/GB]; Roche Products Limited, Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY (GB). CONGREAVE, Miles, Stuart [GB/GB]; Glaxo Wellcome Cambridge Laboratory, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (GB). GORE, Paul, Martin [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GREEN, Darren, Victor, Steven [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HOLMAN, Stuart [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JACK, Torquil, Iain, Maclean [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). KEELING, Steven, Philip [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MASON, Andrew, McMurtrie [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MORRISS, Karen [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). RAMSDEN, Nigel, Grahame [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WARD, Peter [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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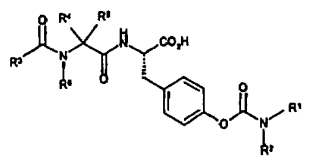
(54) Title: COMPOUNDS USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES



(I)

(57) Abstract

There are provided according to the invention, novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

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Compounds useful in the treatment of inflammatory diseases

This invention relates to novel chemical compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

Integrins are cell surface heterodimeric proteins comprising α and β chains, involved in the inflammatory process. The α4-integrins, which include α4β1 (also known as very late antigen-4 (VLA-4) or CD49d/CD29) and α4β7, are expressed mainly on leukocytes other than neutrophils (eg. eosinophils, T- and B-lymphocytes, basophils and mast cells). The adhesion molecule ligands for α4-integrins include (i) the vascular cell adhesion molecule (VCAM-1; CD106), (ii) a sequence within the alternatively spliced connecting segment-1 (CS-1) in fibronectin (an extracellular matrix protein), and (iii) a site on the mucosal addressin cell adhesion molecule (MAdCAM). Under normal conditions, VCAM-1 is minimally expressed in the vasculature, however, upregulation of VCAM-1 on endothelial cells occurs near sites of inflammation. VCAM-1 has also been identified on a range of non-vascular cells including dendritic cells, bone marrow stromal cells, synoviocytes, astrocytes and some cortical neurons. MAdCAM expression is predominantly associated with gut tissue

being expressed in the high endothelial veins of gut associated lymphoid tissue, peripheral lymph nodes and Peyers Patches.

Both α4β1 (VLA-4) and α4β7 can interact with VCAM-1, CS-1 in fibronectin and MAdCAM. The α4-integrin/VCAM-1 interaction enables adhesion and subsequent transmigration of leukocytes through the wall of post-capillary venules to sites of tissue inflammation. Such an interaction is similarly capable of providing a co-stimulatory signal for T-cell activation, whilst the α4-integrin/fibronectin interaction is believed to have a stimulatory role in the degranulation of mast cells, basophils and eosinophils. Therefore, α4-integrin antagonists are capable of intervention at two levels to effect attenuation of the inflammatory processes which are essential in the pathophysiology of many chronic diseases. These include (i) inhibition of the recruitment of leukocytes to sites of tissue inflammation and (ii) inhibition of the activation of leukocytes and the release of inflammatory mediators.

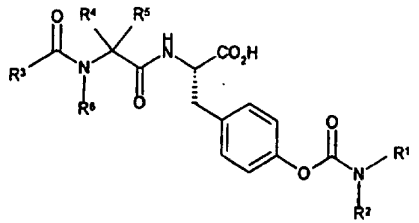
Cell adhesion and signalling, mediated by α4-integrins, are essential in numerous physiological and pathophysiological processes. The therapeutic potential of α4-integrin blocking agents has been investigated previously by testing specific α4-integrin blocking monoclonal antibodies (anti-α4-mAbs) in experimental *in vitro* and *in vivo* models of disease (Lobb and Hemler, 1994). Anti-α4-mAbs have shown beneficial effects in animal models of allergic lung inflammation relevant to asthma, including guinea-pig, rat, rabbit and sheep models. Additionally, anti-α4-mAbs have also been shown to be efficacious in (i) rat and mouse models of experimental allergic encephalomyelitis (considered to be a model of the T-cell dependent autoimmune disease, multiple sclerosis), (ii) mouse models of contact hypersensitivity, (iii) colitis in the Cotton-top tamarin, relevant to inflammatory bowel disease (Podolsky *et al*, 1993), and (iv) insulin dependent diabetes mellitus in the non-obese diabetic mouse (Baron *et al*, 1994). Fibronectin-derived peptides which are thought to block α4-integrin function have shown efficacy in mouse contact hypersensitivity (Ferguson *et al*, 1991) and in rat adjuvant arthritis (Wahl *et al*, 1994).

International patent application numbers WO 98/53814, WO 98/53817 and WO 98/53818 (Merck) describe the use of heterocyclic amide compounds, biarylalkanoic acids and sulphonamide compounds, respectively, as VLA-4 and/or α4/β7 antagonists. WO 98/54207 (Celltech) describes the use of tyrosine derivatives to inhibit the binding of α4 integrins to their ligands for the treatment and prophylaxis of immune or anti-inflammatory disorders.

WO97/03094 (Biogen) describes a selection of semi-peptidic compounds which are capable of inhibiting the binding of ligands to the VLA-4 receptor.

We have now found a novel group of α4-integrin antagonist compounds which antagonise both α4β1 and α4β7 integrins, with the potential to block leukocyte adhesion and activation, consequently effecting anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation. Antagonists of both α4β1 and α4β7 integrins may have advantages over selective antagonists of α4β1 or α4β7 because both integrins are believed to have a role in inflammation.

Thus, according to one aspect of the invention, we provide compounds of formula I:



(I)

wherein R^1 and R^2 independently represent

(i) $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl or $-C_{1-3}$ alkylC_{3-6} cycloalkyl,

or such a group in which alkyl or cycloalkyl is substituted by one or more halogen, -CN, nitro, hydroxy or $-OC_{1-6}$alkyl groups;

(ii) $-(CH_2)_aAr^1$ or $-(CH_2)_aOAr^1$;

or NR^1R^2 together represent pyrrolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, morpholinyl or azepinyl, or such a group fused to a benzene ring, optionally substituted by one or more $-(CO)_n(CH_2)_rAr^1$, $-(CO)_nC_{1-6}$ alkylAr^1Ar^2, $-(CO)_nC_{1-6}$alkyl, $-(CH_2)_rOH$, $-(CH_2)_rO(CH_2)_pOH$, $-(CH_2)_rOC_{1-6}$ alkyl, $-O(CH_2)_rAr^1$, $-(CH_2)_rSO_2Ar^1$, piperidin-1-yl, $-(CH_2)_rCONR^8R^9$, $-NR^{10}(CO)_n(CH_2)_rAr^1$, $-NR^{10}(CO)_nC_{1-3}$alkylC_{3-6} cycloalkyl, $-NR^{10}(CO)_nC_{1-6}$ alkyldiC_{3-6} cycloalkyl, $-CONR^{10}(CH_2)_rAr^1$, halogen, $-NHSO_2C_{1-6}$alkyl, $-SO_2NR^{10}R^{11}$, $-SO_2C_{1-6}$ alkyl or $-SO_2Ar^3$ groups;

R^3 represents $-C_{1-6}$alkylNHC(=NH)NH_2, $-C_{2-6}$alkenylNHC(=NH)NH_2, $-C_{2-6}$alkynylNHC(=NH)NH_2, $-C_{1-6}$alkyl$NR^{14}R^{16}$, $-(CH_2)_nCONR^{14}R^{16}$, $-(CH_2)_nCOC_{1-6}$alkyl, $-(CH_2)_qCHNR^{18}CONR^{20}R^{21}$, $-(CH_2)_mNR^{18}CONR^{14}R^{16}$, $-(CH_2)_qNR^{18}Ar^3$, $-(CH_2)_qCONR^{18}Ar^3$, $-(CH_2)_nCOOR^{19}$, $-(CH_2)_cAr^3$, $-O(CH_2)_cAr^3$, $-(CH_2)_dCO(CH_2)_eAr^3$ or $-(CH_2)_dOAr^3$;

or R^3 represents $-(CH_2)_c$-2,4-imidazolidinedione, $-(CH_2)_c$(piperidin-4-yl), $-(CH_2)_c$(piperidin-3-yl), $-(CH_2)_c$(piperidin-2-yl), $-(CH_2)_c$(morpholin-3-yl) or $-(CH_2)_c$(morpholin-2-yl) optionally substituted on nitrogen by $-(CO)_fC_{1-6}$alkyl, $-(CO)_f(CH_2)_cAr^2$ or $-C(=NH)NH_2$;

or R^3 represents $-(CH_2)_z$dibenzofuran optionally substituted by $-C_{1-6}$alkyl or halogen;

or R^3 represents $-(CH_2)_c$-thioxanthen-9-one;

R^4 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{1-3}$ alkylC_{3-6} cycloalkyl, $-(CH_2)_cAr^2$, $-C_{1-4}$alkyl-X-R^7, $-C_{1-4}$alkyl SO_2C_{1-4} alkyl, $-C_{1-6}$alkyl$NR^{12}R^{13}$ or $-C_{1-6}$ alkyl$NR^{12}COC_{1-6}$ alkyl;

R^5 represents hydrogen, or R^4R^5 together with the carbon to which they are attached form a C_{5-7} cycloalkyl ring;

R^6 represents hydrogen or $-C_{1-6}$alkyl, or R^6 and R^4 together with the N and C atoms to which they are respectively attached form a pyrrolidine ring;

R^7 represents hydrogen, $-(CH_2)_wNR^{12}R^{13}$, $-(CH_2)_vAr^2$ or $-(CH_2)_wNR^{12}COC_{1-6}$ alkyl;

R^8, R^9, R^{16} and R^{17} independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-C_{1-3}$ alkylC_{3-6} cycloalkyl, $-C_{2-6}$alkenyl or NR^8R^9 or $NR^{16}R^{17}$ together represents morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl or piperazinyl N-substituted by $-C_{1-6}$ alkyl, -COphenyl or $-SO_2$methyl;

R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, R^{18}, R^{20} and R^{21} independently represent hydrogen or $-C_{1-6}$alkyl;

R^{14}, R^{19} and R^{22} independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{3-6}$ cycloalkyl or $-(CH_2)_kAr^4$ or $NR^{14}R^{16}$ or $NR^{15}R^{22}$ together represents morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl;

Ar^1 represents phenyl or a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S optionally substituted by one or more halogen, C_{1-6}alkyl, hydroxy, $-OC_{1-6}$alkyl, CF_3, nitro, $-Ar^2$ or $-OAr^2$ groups;

Ar^2 represents phenyl optionally substituted by one or more halogen, $-C_{1-6}$alkyl, hydroxy, $-OC_{1-6}$alkyl, $-CF_3$ or nitro groups;

Ar^3 represents phenyl, a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N or S, or such a group fused to a benzene ring, optionally substituted by one or more $-CO(CH_2)_cAr^4$, $-(CH_2)_rAr^4$, $-(CH_2)_rCOAr^4$, $-(CO)_sC_{1-6}$ alkyl, $-(CO)_sC_{2-6}$ alkenyl, $-(CO)_sC_{2-6}$ alkynyl, $-(CO)_sC_{3-6}$cycloalkyl, $-(CO)_sC_{1-6}$haloalkyl, halogen, $-COCH_2CN$, $-(CH_2)_bNR^{16}R^{17}$, $-(CH_2)_bNHC(=NH)NH_2$, $-CYNR^{16}(CO)_aR^{17}$, $-(CH_2)_bNR^{15}COR^{19}$, $-(CH_2)_bCONR^{15}R^{22}$, $-(CH_2)_bNR^{15}CONR^{15}R^{22}$, $-(CH_2)_bCONR^{15}(CH_2)_fNR^{15}R^{22}$, $-(CH_2)_bSO_2NR^{15}R^{22}$, $-(CH_2)_bSO_2NR^{15}COAr^2$, $-(CH_2)_bNR^{15}SO_2R^{19}$, $-SO_2R^{19}$, $-SOR^{19}$, $-(CH_2)_2OH$, $-COOR^{15}$, -CHO, $-OC_{1-10}$alkyl, $-O(CH_2)_fNR^{15}R^{22}$, $-O(CH_2)_fNHC(=NH)NH_2$, $-O(CH_2)_bCONR^{15}R^{17}$, $-O(CH_2)_kCOOR^{15}$, $-O(CH_2)_fOAr^2$, $-O(CH_2)_bAr^2$, 3-phenyl-2-pyrazolin-5-one or 4,5-dihydro-3(2H)-pyridazinone groups;

Ar^4 represents phenyl or a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S optionally substituted by one or more halogen, $-C_{1-6}$alkyl, hydroxy, $-OC_{1-6}$alkyl, $-CF_3$, nitro or $-CONH_2$ groups;

X and Y independently represent O or S;

a, f, k, s and n independently represent 0 or 1;

b, c, r, x, y and z independently represent an integer 0 to 2;

d, g and u independently represent 1 or 2;

e, h, q and w independently represent an integer 1 to 3;

j and p independently represent an integer 2 to 4;

m independently represents an integer 0 to 4;

t independently represents an integer 0 to 3;

and salts and solvates thereof.

Examples of 5 or 6 membered heterocyclic aromatic rings that Ar^1, Ar^3 and Ar^4 may represent include pyrimidine, pyridine, furan, imidazole, thiophene, pyrrole, thiazole, oxazole, isoxazole, 1,3,4-thiadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole and pyrazole.

Specific examples of 5 or 6 membered heterocyclic aromatic rings that Ar^1 may represent include pyrimidine, pyridine, furan, 1,2,4-thiadiazole and pyrrole.

Specific examples of 5 or 6 membered heterocyclic aromatic rings that Ar^3 may represent include thiazole and pyridine. Phenyl fused to a benzene ring represents naphthyl. An example of a 5 or 6 membered heterocyclic aromatic ring fused to a benzene ring that Ar^3 may represent includes benzofuran.

Specific examples of 5 or 6 membered heterocyclic aromatic rings that Ar^4 may represent include 1,3,4-thiadiazole, 1,2,3-thiadiazole, 1,2,4-oxadiazole and pyrazole.

We prefer R^1 and R^2 to be defined such that NR^1R^2 together represent piperidinyl, piperazinyl, thiomorpholinyl, morpholinyl or 1,2,3,4-tetrahydroisoquinoline optionally substituted by a $-(CO)_n(CH_2)_rAr^1$, $-(CO)_nC_{1-6}$alkyl, $-(CH_2)_tCONR^8R^9$, $-NR^{10}(CO)_n(CH_2)_rAr^1$, $-NR^{10}(CO)_nC_{1-3}$ alkylC_{3-6} cycloalkyl, $-NR^{10}(CO)_nC_{1-6}$ alkyldiC_{3-6} cycloalkyl, $-(CH_2)_tOC_{1-6}$ alkyl, $-(CH_2)_tO(CH_2)_pOH$, piperidin-1-yl, $-(CH_2)_tOH$ or $-CONR^{10}(CH_2)_rAr^1$ group.

We particularly prefer R^1 and R^2 to be defined such that NR^1R^2 together represents morpholinyl or piperazinyl optionally N-substituted by $-(CO)_nC_{1-6}$ alkyl (especially $-COCH_3$), piperazinyl N-substituted by $-(CO)_n(CH_2)_rAr^1$ (especially -COphenyl and $-(CO)_2$-furanyl), piperidinyl substituted by $-NR^{10}(CO)_n(CH_2)_rAr^1$ (especially $-NHCOCH_2$phenyl) or piperidinyl substituted by $-(CH_2)_tCONR^8R^9$ (especially $-CONH_2$).

We prefer R^3 to represent $-(CH_2)_c$-2,4-imidazolidinedione-3-yl, $-(CH_2)_c$-thioxanthen-9-one-3-yl, $-(CH_2)_cAr^3$, $-O(CH_2)_cAr^3$, $-(CH_2)_cOAr^3$ or $-(CH_2)_t$dibenzofuran, particularly $-OCH_2Ar^3$, $-CH_2OAr^3$ or dibenzofuran, especially $-CH_2OAr^3$ or dibenzofuran.

When R^3 represents $-(CH_2)_t$dibenzofuran (particularly dibenzofuran), we prefer it to represent $-(CH_2)_c$-2-dibenzofuran (particularly 2-dibenzofuran).

When R^3 represents $-(CH_2)_c$-2,4-imidazolidinedione, we prefer it to represent $-(CH_2)_c$-(2,4-imidazolidinedione-3-yl) (particularly $-CH_2$-2,4-imidazolidinedione-3-yl).

When R^3 represents $-(CH_2)_c$-thioxanthen-9-one, we prefer it to represent $-(CH_2)_c$-(thioxanthen-9-one-3-yl) (particularly $-CH_2$-thioxanthen-9-one-3-yl).

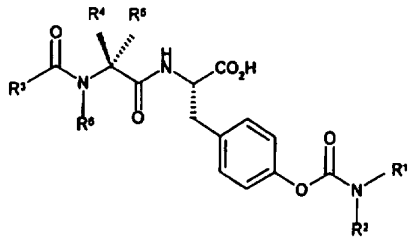
We most especially prefer R^3 to represent $-CH_2OAr^3$.

We prefer R^4 to represent $-C_{1-6}$ alkyl, R^5 to represent hydrogen or for R^4R^5, together with the carbon to which they are attached, to form a cyclohexyl ring, and for R^6 to represent hydrogen or methyl (particularly hydrogen).

We particularly prefer R^4 to represent $-C_{1-6}$ alkyl, and for R^5 and R^6 to represent hydrogen.

We especially prefer R^4 to represent $-CH_2CHMe_2$ and for R^5 and R^6 to represent hydrogen.

We particularly prefer R^4 and R^5 to have the stereochemical orientation shown in formula (Ia):



(Ia)

We prefer R^7 to represent $-(CH_2)_rAr^2$ or $-(CH_2)_rNR^{12}COC_{1-6}$ alkyl.

We especially prefer R^8 and R^9 each to represent hydrogen or for NR^8R^9 together to represent piperidinyl or pyrrolidinyl, particularly piperidinyl.

We prefer R^{10} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{11} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{12} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{13} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{14} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{15} to represent hydrogen or $-C_{1-6}$ alkyl, particularly hydrogen.

We prefer R^{16} to represent hydrogen, $-C_{1-4}$ alkyl or $-C_{2-4}$ alkenyl, particularly hydrogen or propenyl.

We prefer R^{17} to represent hydrogen, $-C_{1-4}$ alkyl or $-C_{2-4}$ alkenyl, particularly hydrogen, methyl or propenyl.

We prefer R^{18} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{19} to represent hydrogen or $-C_{1-6}$ alkyl, particularly $-C_{1-4}$ alkyl, especially methyl.

We prefer R^{20} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{21} to represent hydrogen or methyl, particularly hydrogen.

We prefer R^{22} to represent hydrogen, $-C_{1-4}$ alkyl or $-(CH_2)_eAr^4$ or for $NR^{15}R^{22}$ together to represent piperidinyl, pyrrolidinyl or morpholinyl.

We especially prefer R^{15} and R^{22} to be defined such that $NR^{15}R^{22}$ together represents piperidinyl.

We prefer Ar^1 to represent furan, pyrimidine or phenyl optionally substituted by halogen (eg. chlorine or fluorine) or $-OC_{1-6}$ alkyl.

We prefer Ar^2 to represent unsubstituted phenyl.

We prefer Ar^3 to represent phenyl, naphthyl or benzofuran optionally substituted by one or more $-(CH_2)_yCOAr^4$, $-COOR^{15}$, $-(CH_2)_bSO_2NR^{15}R^{22}$, $-(CH_2)_bNR^{15}SO_2R^{19}$, $-SO_2R^{19}$, $(CO)_aC_{2-6}$ alkenyl, $-(CO)_aC_{1-6}$ alkyl, $-(CO)_aC_{3-6}$cycloalkyl, halogen, $-(CH_2)_bCONR^{15}R^{22}$, 3-phenyl-2-pyrazolin-5-one-2-yl or 4,5-dihydro-3(2H)-pyridazinone-6-yl groups. We particularly prefer Ar^3 to represent phenyl or naphthyl optionally substituted by $-(CO)_aC_{1-6}$ alkyl, $-(CO)_aC_{3-6}$ cycloalkyl, halogen, $-(CH_2)_yCOAr^4$ or $-(CH_2)_bCONR^{15}R^{22}$.

We most particularly prefer Ar^3 to represent phenyl substituted by n-propyl, tertiary butyl, cyclohexyl, Iodine, -COphenyl or COpiperidin-1-yl or naphthyl substituted by COpiperidin-1-yl.

We prefer Ar^4 to represent phenyl or furan optionally substituted by halogen, especially unsubstituted phenyl or furan.

We prefer e to represent 1 or 2.

We prefer n to represent 0 or 1.

We prefer r to represent 0 or 1, particularly 1.

We prefer p to represent 2.

We prefer t to represent 0, 1 or 3, particularly 0 or 1, especially 0.

We prefer h to represent 1 or 2, particularly 2.

We prefer d to represent 1.

We prefer m to represent 0 or 1, particularly 1.

We prefer c to represent 0 or 1, particularly 1.

We prefer f to represent 1.

We prefer q to represent 1 or 2, particularly 1.

We prefer u to represent 1.

We prefer w to represent 1 or 2, particularly 1.

We prefer x to represent 0 or 1, particularly 1.

We prefer a to represent 0.

We prefer y to represent 0 or 1, particularly 0.

We prefer b to represent 0 or 1, particularly 0.

We prefer j to represent 2 or 3, particularly 2.

We prefer z to represent 0 or 1, particularly 0.

We prefer k to represent 1.

We prefer s to represent 0.

We prefer g to represent 1.

We prefer X to represent oxygen.

We prefer Y to represent oxygen.

The most preferred compounds of formula (I) are:

(2S)-2-{[(2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-3-{4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid;

(2S)-2-{[(2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy] phenyl}propanoic acid;

(2S)-3-{4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino]propanoic acid;

(2S)-3-{4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid;

(2S)-3-{4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{((2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid;

(2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino)-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-2-({(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino]propanoic acid;

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid;

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino) propanoic acid;

and salts and solvates thereof.

The following compounds are also particularly preferred

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-2-{[2-(2-benzoylphenoxy)acetyl]amino}-4-methylpentanoyl)amino] propanoic acid;

(2S)-2-[[(2S)-2-({2-[4-(Aminocarbonyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid;

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino} propanoic acid;

and salts and solvates thereof.

The above preferred compounds are characterised by low oral bioavailability which is an advantageous property for an inhaled medicine in order to minimise potential side effects.

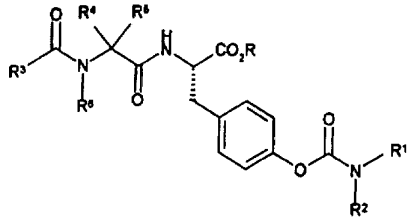
Suitable salts of the compounds of formula (I) include physiologically acceptable salts such as alkali metal salts, for example calcium, sodium and potassium salts and salts with (trishydroxymethyl)aminomethane. Other salts of the compounds of formula (I) include salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxynathanoate, methanesulphonate. Examples of solvates include hydrates.

When sidechains of compounds of formula (I) contain chiral centres, the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as to individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a purified single enantiomer.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises:

(a) hydrolysis of a carboxylic acid ester of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above and R is a group capable of forming a carboxylic acid ester; or

(b) deprotecting a compound of formula (I) which is protected.

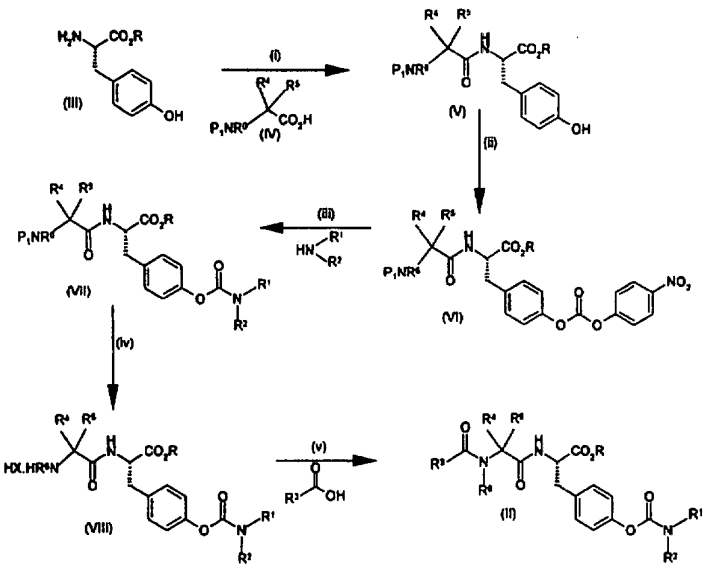
In process (a) an example of a suitable R group is a C_{1-6} alkyl group such as methyl or t-butyl. Hydrolysis may either occur via an acidic process e.g. involving trifluoroacetic acid and water or via an alkaline route e.g. utilising sodium hydroxide and methanol.

In an alternative solid phase reaction, R may represent a solid support functionalised with available hydroxy groups. Examples of solid supports include resins such as polystyrene resins wherein phenyl rings are provided with hydroxy groups via linkers. An example of a hydroxy functionalised linker is $-CH_2O$(4-hydroxymethyl-phenyl) (Wang Resin) or an N-Fmoc amino acid acyl ester of 3-methoxy-4-oxymethyl-phenoxymethylated 1% divinylbenzene cross-linked polystyrene (Sasrin resin).

In process (b) examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate.

Compounds of formula (II) may be prepared following Scheme 1;

Scheme 1



Step (i) In this Scheme we prefer R to represent methyl.

Compounds of formula (III) and (IV) may be reacted under conventional conditions for preparation of an amide. Desirably a coupling agent eg. WSCDI with or without HOBT in an inert solvent such as MeCN or DMF is used. P_1 is an amine protecting group such as one described previously under process (b). In this Scheme we prefer P_1 to represent Boc.

Step (ii) The conversion of formula (V) to (VI) is suitably carried out with p-nitrophenylchloroformate under conventional conditions eg. in the presence of an organic base, eg. pyridine and an inert organic solvent such as DCM.

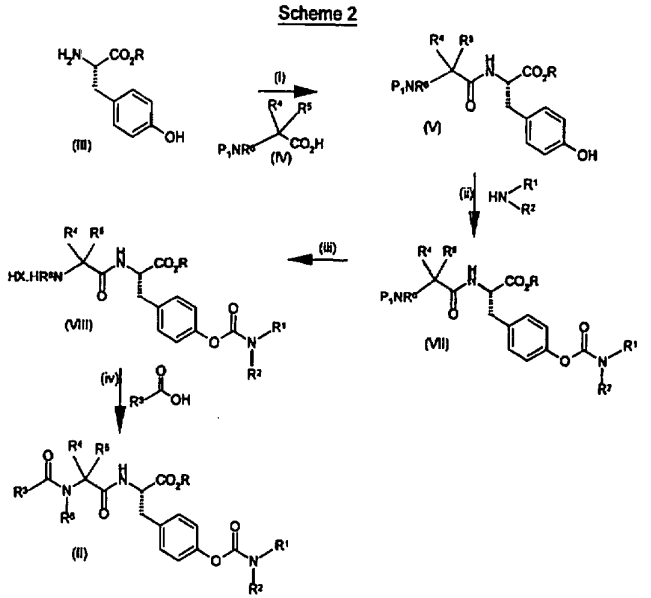
Step (iii) This reaction may be performed by combination of the reagents in a suitable solvent, such as DCM in the presence of an organic base such as DIPEA.

Step (iv) This deprotection step may be performed under conventional conditions. When P_1 represents Boc, it may be removed by treatment with acid e.g. a hydrohalic acid (HX) such as HCl.

Step (v) A condensation reaction of formula (VIII) with the compound of formula R^3CO_2H may be performed under conditions similar to those described above for step (i).

An alternative process for preparation of compounds of formula (II) is given in Scheme 2 below:

Scheme 2



Step (i) In this Scheme we prefer R to represent t-Bu. The reaction conditions for this step are analogous to those for Scheme 1 step (i).

In compounds of formula (IV) in this Scheme we prefer P^1 to represent Cbz.

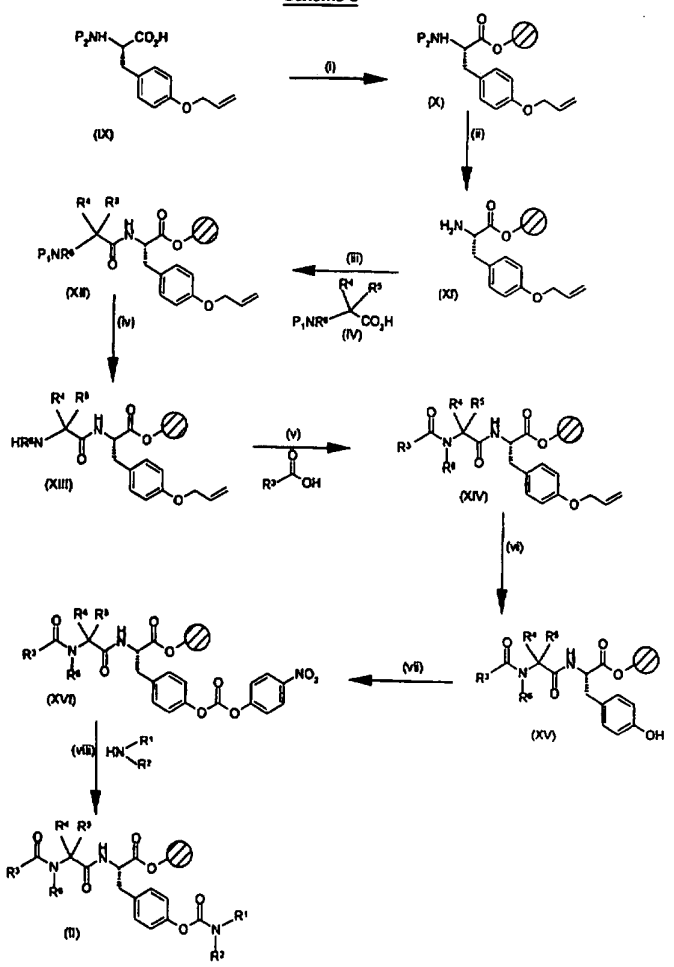
Step (ii) This process comprises a two stage reaction, consisting of (a) treatment with a carboxyl donor such as $(Cl_3CO)_2CO$ typically in the presence of an organic base such as DIPEA and a suitable solvent, such as THF or DCM followed by (b) conversion to the carbamate by treatment with R^1R^2NH in a process analogous to that described previously in Scheme 1 step (iii).

Step (iii) This deprotection reaction can be performed under conventional conditions. When P_1 represents Cbz, deprotection may be achieved by hydrogenolysis e.g. by treatment with ammonium formate in the presence of Pd/C in a solvent such as ethanol. The reaction may be worked up with acid, such as a hydrohalic acid to give the product as a hydrohalic acid salt (e.g. the HCl salt).

Step (iv) This process is analogous to Scheme 1, step (v).

An alternative process for preparation of compounds of formula (II) is given in Scheme 3 below:

Scheme 3



Step (i) P_2 is an amine protecting group such as one described previously and in this Scheme we prefer P_2 to represent Fmoc. More preferably P_2 will be Boc.

A compound of formula (IX) may be reacted onto a suitable solid phase, such as a hydroxy functionalised polystyrene resin (e.g. Wang or Sasrin resin) in the presence of 2,6-dichlorobenzoyl chloride, pyridine and a suitable solvent, such as DMF.

Step (ii) Removal of N-protecting group P_2 may be achieved under conventional conditions; e.g. when P_2 represents Fmoc, by treatment with an organic base such as piperidine in a suitable solvent, such as DMF or eg. when P_2 represents Boc, by treatment with chlorotrimethylsilane and phenol in a suitable solvent such as DCM.

Step (iii) In this Scheme, P_1 may suitably represent Fmoc. Alternatively, it may suitably represent Boc. Reaction of a compound of formula (XI) with the compound of formula (IV) to produce an amide, may be performed in the presence of a coupling agent, such as PyBop, an organic base, such as DIPEA and a suitable solvent, such as DMF.

Step (iv) This de-protection reaction may be performed under conventional conditions eg. when P_1 represents Fmoc or Boc, under conditions analogous to those described above for step (ii).

Step (v) A condensation reaction of formula (XIII) with the compound of formula R^3CO_2H may be performed in the presence of a suitable coupling agent, such as PyBop, an organic base, such as DIPEA and a suitable solvent, such as DMF.

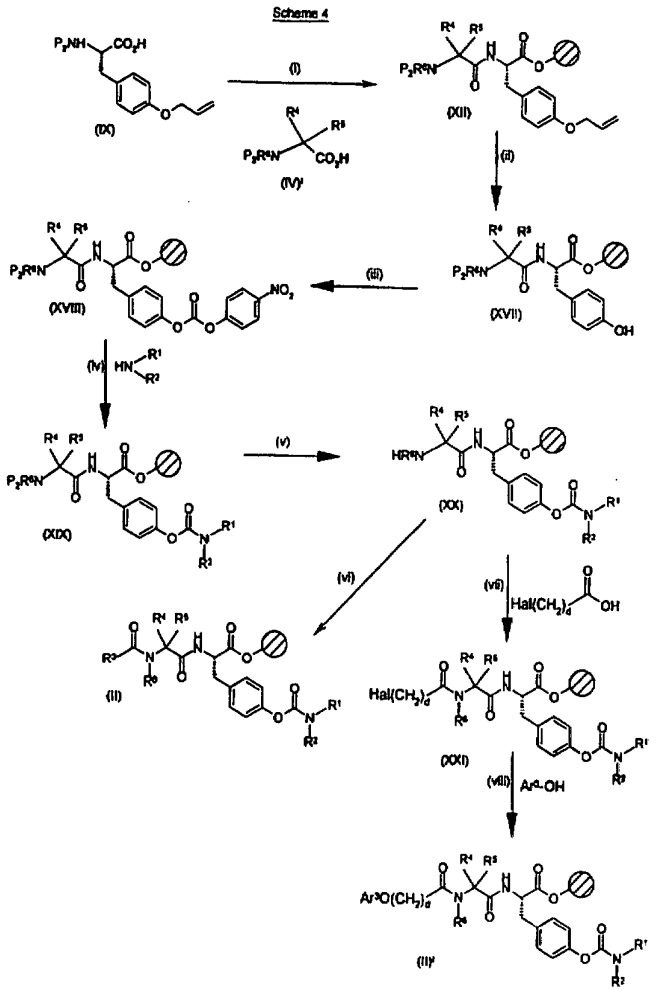
Step (vi) This step comprises an alkenyl chain cleavage reaction on the compound of formula (XIV) to produce a compound of formula (XV), eg. by the treatment with $Pd(PH_3)_4$ and $PhSiH_3$ (or morpholine) in the presence of a suitable solvent, such as DCM.

Step (vii) The conversion of a compound of formula (XV) to a compound of formula (XVI) is suitably performed by treatment with p-nitrophenyl chloroformate, under conventional conditions, in the presence of an organic base, such as DIPEA and an inert organic solvent, such as THF and/or DCM.

Step (viii) This reaction may be performed by combination of the reagents in the presence of an organic base, such as DIPEA and suitable solvents, such as DCM and/or THF.

An alternative process for preparation of certain compounds of formula (II) is given in Scheme 4 below:

Scheme 4



Step (i) In this Scheme we prefer P_2 to represent Fmoc.

This conversion may be achieved following processes analogous to those of Scheme 3 steps (i) to (iii).

Step (ii) An alkenyl chain cleavage reaction may be performed by a process analogous to Scheme 3 step (vi).

Step (iii) A p-nitrophenyl carbonate formation reaction, may be performed with reaction conditions analogous to Scheme 3 step (vii).

Step (iv) The conversion of formula (XVIII) to (XIX) can be performed by a reaction analogous to Scheme 3 step (viii).

Step (v) This de-protection reaction may be performed using an analogous process to Scheme 3 step (ii).

Step (vi) The conversion of formula (XX) to (II) can be performed by a condensation reaction in the presence of a suitable acid, employing a suitable coupling agent, such as PyBop, an organic base, such as DIPEA and a solvent, such as DMF.

Compounds of formula (II) in which R^3 represents $-(CH_2)_dOAr^3$ may alternatively be prepared from compounds of formula (XX) following steps (vii) and (viii):

Step (vii) The conversion of formula (XX) to (XXI) can be performed by a condensation reaction in the presence of a haloalkanoic acid (such as the bromo derivative i.e. Hal represents bromine), employing a suitable coupling agent, such as DIC and a solvent, such as DMF.

Step (viii) In this step, the reaction of a compound of formula (XXI) with a compound of formula Ar^3-OH group may be undertaken in the presence of potassium carbonate, sodium iodide and a suitable solvent, such as DMF.

Compounds of formula III, IV, IV', HNR^1R^2, R^3COOH, IX, $Hal(CH_2)_dCOOH$ and Ar^3-OH are either known or may be prepared by known methods.

Compounds of the invention may be tested for *in vitro* and *in vivo* biological activity in accordance with the following assays.

(1) Jurkat J6/VCAM-1 Adhesion Assay

This assay was used to investigate the interaction of the integrin VLA-4, expressed on the Jurkat J6 (human lymphoblast cell line) cell membrane with VCAM-1. Polystyrene 96-well microtitre plates were coated with human immunoglobulin G (IgG; Sigma Chemicals, UK, Product No. I4506) at a concentration of 0.05mg ml^{-1} in bicarbonate buffer (36mM $NaHCO_3$ and 22mM Na_2CO_3, prepared in Dulbecco's phosphate buffered saline at pH 9.8 (PBS); Sigma Chemicals, UK, Product No. 14190-094) for 2 hours at 37°C. This solution was then aspirated and the plates were washed twice with PBS.

VCAM-1 was prepared by cloning its constituent seven domains into a Drosophila expression system with a zz (Protein A) tag. This zzVCAM-1 was then expressed from *Drosophila melanogaster* S2 cell culture, induced with copper. Protease inhibitors were added and the culture supernatant was clarified either by filtration through a 0.2μm filter or by centrifugation. The zzVCAM-1 was then purified from this clarified medium using an IgG agarose column, equilibrated with either 20mM sodium phosphate pH 7.2 alone or in the presence of 0.5M sodium chloride. Elution of zzVCAM-1 from the column was mediated using 3M ammonium thiocyanate, which was subsequently removed using a G25 desalting column, equilibrated with 20mM sodium phosphate, pH 7.2. The purified zzVCAM-1 was then concentrated to a small volume (Amicon stirred cell concentrators) until a concentration of 62.5ng ml^{-1} was obtained, calculated using the extinction coefficient value.

This solution of zzVCAM-1 was then incubated overnight at 4°C in the IgG coated microtitre plates with 3% bovine serum albumin (BSA) in PBS, followed by aspiration and two further washes with PBS. A concentration of the Jurkat J6 cells (6 x 10^6 cells ml^{-1}), grown in cell media RPMI 1640 (HyClone Ltd, Product No. B-9106-L) supplemented with 10% heat inactivated foetal calf serum (FCS; Gibco BRL, Product No. 10099-075) and 2mM L-glutamine, were labelled with 10μM of the fluorescent dye, 2', 7'-bis(2-carboxyethyl)-5-(e6)-carboxyfluorescein acetoxymethyl ester (BCECF-AM; Molecular Probes Inc, Product No. B-1150) at 37°C for 10 minutes. The excess dye was then removed by centrifugation at 500xg for 5 minutes and the cells were resuspended at a concentration of 1.2 x 10^7 cells ml^{-1} in Hank's balanced salt solution (HBSS; Gibco BRL, Product No. 14190-094).

Equal volumes of compounds (dissolved in an appropriate solvent and diluted in HBSS containing 1mM $MnCl_2$) and the labelled Jurkat J6 cells, were added to the VCAM-1 coated plates and adhesion was allowed to proceed for 30 minutes at 37°C. Non, or loosely adhered cells, were removed by inversion of the plate and blotted with tissue paper. Two washes with PBS and further blotting were then performed, before the addition of 2% detergent (Triton-X®; Sigma Chemicals UK, Product No. X100). Counting was undertaken in a Wallac Viktor™ Fluorimeter, where low fluorescence values were indicative of compounds which had inhibited adhesion. All samples were assayed in singlicate and the following four parameter curve fit, shown by Equation (I) was applied:

Equation (I)

$$y = \frac{a - d}{1+\left(\frac{x}{c}\right)^b} + d$$

Where a is the minimum, b is the Hill slope, c is the IC_{50} and d is the maximum. (Maximum and minimum values are those compared to adhesion in the absence of compound and in the presence of the dipotassium salt of 2mM EDTA; Sigma Chemicals, UK, Product No. ED2P). Data is presented as the mean pIC_{50} with the standard error of the mean of n experiments.

(2) CD3/VCAM-1 Co-stimulation of T-Lymphocyte Proliferation

$CD4^+$ T-cells were purified from peripheral blood mononuclear cells by negative selection with anti-CD14, CD19, CD16 and HLA.DR antibodies and Dynal beads. Flat bottomed 96-well tissue culture plates were coated with 1μg ml^{-1} anti-CD3 antibody (OKT3), washed and incubated with human IgG and zzVCAM-1 fusion proteins. The $CD4^+$ T cells (prepared in RPMI-1640 medium supplemented with 10% FCS, penicillin or streptomycin and L-glutamine) were added to the coated plates (1 x 10^5 cells $well^{-1}$) and incubated in the presence or absence of various doses of compound or blocking antibodies for 4 days. Radiolabelled thymidine [^{3}H] was added for the final 6 hours of incubation and the cells were then harvested using a Skatron plate harvester. Incorporation of the [^{3}H] label was measured as an indicator of T cell proliferation using a β plate counter. Compounds were assayed in triplicate and data was collected in an analogous procedure to that described for Assay (1).

(3) Inhibition of Eosinophil Infiltration and Hyper-Reactivity in the Guinea Pig

In a method based on that described by Danahay *et al.*, 1997, ovalbumin sensitised guinea pigs were dosed with mepyramine (30mg kg^{-1} ip) to protect against anaphylactic bronchospasm. Test compounds, dissolved in 0.9% saline, were given by the inhaled route (30 minutes breathing of an aerosol of the compound) or the intra-tracheal route, 30 minutes before and 6 hours after ovalbumin challenge (10 minutes breathing of an aerosol generated from a 0.5% solution of ovalbumin). Hyper-reactivity of the airways to the thromboxane mimetic U46619, was measured 24 hours after ovalbumin challenge in un-restrained animals using a whole body plethysmograph (Buxco Ltd., USA). The guinea pigs were then sacrificed and the lungs lavaged. Total and differential leukocyte counts were then obtained for the bronchoalveolar lavage fluid and the percentage reduction in eosinophil accumulation determined (Sanjar *et al.*, 1992). Dexamethasone (200μg kg^{-1} i.t) was used as a positive control. Data was presented as the inhibitory effect of the specified dose expressed as a percentage of the vehicle control response.

(4) RPMI 8866/MAdCAM-1 Adhesion Assay

This assay was used to investigate the interaction of the integrin $\alpha_4\beta_7$, expressed on the RPMI 8866 (human B lymphoid cell line) cell membrane with MAdCAM-1. Polystyrene 96-well microtitre plates were coated with human immunoglobulin G (IgG; Sigma Chemicals, UK, Product No. I4506) at a concentration of 0.05mg ml^{-1} in bicarbonate buffer (36mM $NaHCO_3$ and 22mM Na_2CO_3, prepared in Dulbecco's phosphate buffered saline at pH 9.8 (PBS); Sigma Chemicals, UK, Product No. 14190-094) for 2 hours at 37°C. This solution was then aspirated and the plates were washed twice with PBS.

MAdCAM-1 was prepared by cloning its constituent domains, under the control of a polyhedrin promoter, into a baculovirus expression system with a zz (Protein A) tag. The amplified baculovirus containing zzMAdCAM-1 was used to infect *Spodoptera frugiperda* cells growing in suspension in SF900II medium supplemented with 5% foetal calf serum. The cells were infected at a multiplicity of infection of 1 and harvested 48 hours later by centrifugation. Protease inhibitors were added and the culture supernatant was clarified either by filtration through a 0.2µm filter or by centrifugation. The zzMAdCAM-1 was then purified from this clarified medium using an IgG agarose column, equilibrated with either 20mM sodium phosphate pH 7.2 alone or in the presence of 0.5M sodium chloride. Elution of zzMAdCAM-1 from the column was mediated using 3M ammonium thiocyanate. The sample was then dialysed thoroughly, using 20mM sodium phosphate pH 7.2, to remove the ammonium thiocyanate. The purified zzMAdCAM-1 was then concentrated to a small volume (Amicon stirred cell concentrators) until a concentration of 0.5mg ml^{-1} was obtained, calculated using the extinction coefficient value.

This solution of zzMAdCAM-1 was diluted 1:2500 and then incubated overnight at 4°C in the IgG coated microtitre plates with 3% bovine serum albumin (BSA) in PBS, followed by aspiration and two further washes with PBS. A concentration of the RPMI 8866 cells (3×10^6 cells ml^{-1}), grown in cell media RPMI 1640 (HyClone Ltd, Product No. B-9106-L) supplemented with 10% heat inactivated foetal calf serum (FCS; Gibco BRL, Product No. 10099-075) and 2mM L-glutamine, were labelled with 10µM of the fluorescent dye, 2', 7'-bis(2-carboxyethyl)-5-(e6)-carboxyfluorescein acetoxymethyl ester (BCECF-AM; Molecular Probes Inc, Product No. B-1150) at 37°C for 10 minutes. The excess dye was then removed by centrifugation at 500xg for 5 minutes and the cells were resuspended at a concentration of 6×10^6 cells ml^{-1} in Hank's balanced salt solution (HBSS; Gibco BRL, Product No. 14190-094).

Equal volumes of compounds (dissolved in an appropriate solvent and diluted in HBSS containing 1mM $MnCl_2$) and the labelled RPMI 8866 cells, were added to the MAdCAM-1 coated plates and adhesion was allowed to proceed for 30 minutes at 37°C. Non, or loosely adhered cells, were removed by inversion of the plate and blotted with tissue paper. Two washes with PBS and further blotting were then performed, before the addition of 2% detergent (Triton-X®; Sigma Chemicals UK, Product No. X100). Counting was undertaken in a Wallac Victor™ Fluorimeter, where low fluorescence values were indicative of compounds which had inhibited adhesion. All samples were assayed in singlicate and the following four parameter curve fit, shown by Equation (I) (above) was applied. Wherein the maximum and minimum values are those compared to adhesion in the absence of compound and in the presence of the dipotassium salt of 2mM EDTA; Sigma Chemicals, UK, Product No. ED2P). Data is presented as the mean pIC_{50} with the standard error of the mean of n experiments.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD) and rhinitis. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure. Furthermore, compounds of the invention may be used to treat nephritis, skin diseases such as psoriasis, allergic dermatitis and hypersensitivity reactions and diseases of the central nervous system which have an inflammatory component eg. Alzheimer's disease, meningitis, multiple sclerosis and AIDS dementia.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome.

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as pharmaceuticals, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as pharmaceuticals, particularly in the treatment of patients with inflammatory conditions.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration, preferably for topical administration to the lung, eg. by aerosol or as a dry powder composition.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium

lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator, solutions for nebulisation or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents. Powder compositions for inhalation will preferably contain lactose. Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges of for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (eg. fluticasone propionate, beclomethasone dipropionate, mometasone

furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg. antibiotics, antivirals).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example an anti-inflammatory agent such as a corticosteroid, NSAID, beta adrenergic agent or an anti-infective agent. A pharmaceutical composition comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in combination together with a long acting β_2 adrenergic receptor agonist (eg. salmeterol or a salt or solvate thereof such as salmeterol xinafoate) is of particular interest.

The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of the invention have the advantage that they may be more efficacious, show greater selectivity (eg. in that they selectively antagonise $\alpha 4$ integrins relative to $\beta 2$ integrins such as LFA-1 or VLA-5 ($\alpha v \beta 1$)), have fewer side effects, have a longer duration of action, be less bioavailable or show less systemic activity when administered by inhalation, have ready and economic synthesis, or have other more desirable properties than similar known compounds.

Certain intermediates are new and provide a further aspect of the invention.

The invention may be illustrated by reference to the following examples:

Examples

General Experimental Details

Where compounds were purified by "flash column chromatography on silica gel" this refers to the use of silica gel, 0.040 to 0.063mm mesh (e.g. Merck Art 9385), where column elution is accelerated by an applied pressure of nitrogen at up to 5 p.s.i. Where thin layer chromatography (TLC) has been used this refers to silica gel TLC using 5 x 10 cm silica gel plates (e.g. Polygram SIL G/UV_{254}).

Mass Spectroscopy

Mass Spectrometry (MS) was carried out using an HP5989A Engine Mass Spectrometer connected to a flow inject system (0.05M aqueous ammonium acetate/methanol (35:65) at a flow rate of 0.7 ml/min) with positive thermospray ionisation.

NMR

NMR spectra were run on a Bruker DPX400 400MHz spectrometer.

LC/MS System

The Liquid Chromatography Mass Spectrometry (LCMS) system used was as follows: -

A 3µm ABZ+PLUS, 3.3cm x 4.6mm internal diameter column eluting with solvents: A –0.01M Aqueous ammonium acetate + 0.1%v/v formic acid, and B - 95:5 acetonitrile/water + 0.05%v/v formic acid with a flow rate of 3ml/min. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 - 100% B over 3.7 mins; hold at 100% B for 0.9 mins; return to 0% B over 0.2 mins.

Positive and negative electrospray ionisation was employed.

Protection Measurement

The method for measuring the substitution of Fmoc-amino acid resins was as follows:-

To 10mg of resin was added 20% piperidine in DMF (1ml). After shaking for 30 mins at 20°C the resin was filtered. To 50µL of the filtrate was added 20% piperidine in DMF (0.95ml) and the absorbance of the solution was measured at 302nm using a UV spectrophotometer. Substitution was calculated using the following equation:-

Substitution (mmol/g) = (Absorbance x 2 x 10^4) / (Extinction coefficient x weight in mg)

Intermediates

Intermediate 1: Methyl (2S)-2-(((2S)-2-[(tert-butoxycarbonyl)amino]-4-methyl pentanoyl)amino)-3-(4-hydroxyphenyl)propanoate

To a solution of N-(*tert*-butoxycarbonyl)-L-leucine (7g) in acetonitrile (100ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.9g) and 1-hydroxybenzotriazole (4.2g). After stirring for 30 mins at 20°C L-tyrosine methyl ester (5.5g) was added and stirring was continued for 18h. The mixture was concentrated *in vacuo* to *ca.* 10ml and the residue was partitioned between 1M hydrochloric acid (200ml) and ethyl acetate (100ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (100ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (100ml), water (2 x 100ml) and brine (50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with chloroform to give the title compound as a white foam (11.3g, 98%). LCMS: R_t 3.11 min; *m/z* 409 (MH^+).

Intermediate 2: Methyl (2S)-2-[[(2S)-2-amino-4-methylpentanoyl]amino)-3-(4-hydroxyphenyl)propanoate hydrochloride

To a solution of Intermediate 1 (3.1g) in 1,4-dioxane (10ml) was added 4M hydrogen chloride in 1,4-dioxane (20ml). The solution was stirred for 2h at 20°C then evaporated *in vacuo*. The residue was co-evaporated with toluene (2 x 20ml) and ether (2 x 20ml) to give the title compound as a white solid (2.6g, 98%). LCMS: R_t 1.98 min; *m/z* 309 (MH^+).

Intermediate 3: Methyl (2S)-3-(4-hydroxyphenyl)-2-(((2S)-4-methyl-2-[(2-[[3-(1-piperidinylcarbonyl)-2-naphthyl]oxy}acetyl)amino]pentanoyl)amino)propanoate

To a suspension of Intermediate 44 (0.45g) in acetonitrile (20ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.31g) and 1-hydroxybenzotriazole (0.22g). After stirring for 30 mins at 20°C Intermediate 2 (0.5g) was added followed by diisopropylethylamine (0.28ml) and stirring was continued for 18h. The mixture was concentrated *in vacuo* and the residue was partitioned between 2M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (30ml), water (2 x 30ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with ethyl

acetate/petroleum ether (2:1) to give the title compound as a white foam (0.6g, 69%). LCMS: R_t 3.42 min; *m/z* 604 (MH^+).

Intermediate 4: Methyl (2S)-3-(4-hydroxyphenyl)-2-[((2S)-2-[[2-(2-iodophenoxy) acetyl]amino]-4-methylpentanoyl)amino]propanoate

This was similarly prepared from Intermediate 43 (0.81g) and Intermediate 2 (1.02g). The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give the title compound as a white foam (1.2g, 74%). LCMS: R_t 3.40 min; *m/z* 569 (MH^+).

Intermediate 5: Methyl (2S)-2-{{(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)-3-(4-hydroxyphenyl)propanoate

This was similarly prepared from Intermediate 45 (0.29g) and Intermediate 2 (0.5g). The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give the title compound as a white foam (0.66g, 97%). LCMS: R_t 3.55 min; *m/z* 503 (MH^+).

Intermediate 6: Methyl (2S)-2-{{(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)-3-(4-[[(4-nitrophenoxy)carbonyl]oxy)phenyl)propanoate

To a solution of Intermediate 5 (0.59g) in dichloromethane (5ml), under a nitrogen atmosphere, was added 4-dimethylaminopyridine (0.18g). The mixture was cooled to 0-5°C and 4-nitrophenyl chloroformate (0.3g) was added. Stirring was continued for 18h allowing the reaction to warm to 20°C. The solution was diluted with chloroform (60ml) and washed with 1M hydrochloric acid (2 x 40ml) and water (40ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with cyclohexane/ethyl acetate (3:2) to give the title compound as a white foam (0.36g, 46%). LCMS: R_t 3.98 min; *m/z* 668 (MH^+).

Intermediate 7: 4-[(2S)-2-{((2S)-2-[(Tert-butoxycarbonyl)amino]-4-methyl pentanoyl)amino)-3-methoxy-3-oxopropyl]phenyl 4-[(2-phenylacetyl)amino]-1-piperidinecarboxylate

To a solution of triphosgene (0.59g) in anhydrous dichloromethane (40ml), under a nitrogen atmosphere, was added a solution of Intermediate 1 (1.67g) in anhydrous dichloromethane (10ml) followed by diisopropylethylamine (1.2ml). After stirring for 3h at 20°C Intermediate 59 (1g) was added followed by diisopropylethylamine (0.8ml). Stirring was continued for 18h then the mixture was evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1 switching to 5:1) to give the title compound as a white solid (1.76g, 59%).

LCMS: R_t 3.42 min; *m/z* 651 $[M-H]^-$.

Intermediate 8: 4-{(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino)-3-methoxy-3-oxopropyl)phenyl 4-[(2-phenylacetyl)amino]-1-piperidinecarboxylate hydrochloride

To a solution of Intermediate 7 (1.76g) in 1,4-dioxane (10ml) was added 4M hydrogen chloride in 1,4-dioxane (8ml). After stirring for 3h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a cream solid (1.59g, 100%). LCMS: R_t 2.50 min; *m/z* 553 (MH^+).

Intermediate 9: Methyl (2S)-2-{{(2S)-2-[(tert-butoxycarbonyl)amino]-4-methyl pentanoyl}amino)-3-(4-[[(4-nitrophenoxy)carbonyl]oxy)phenyl)propanoate

To a solution of Intermediate 1 (0.41g) in dichloromethane (3ml), under a nitrogen atmosphere, was added pyridine (1ml). The mixture was cooled to 0-5°C and 4-nitrophenyl chloroformate (0.22g) was added. Stirring was continued for 18h allowing the reaction to warm to 20°C. The solution was diluted with dichloromethane (40ml) and washed with 1M hydrochloric acid (50ml). The aqueous phase was further extracted with dichloromethane (40ml) and the combined organic extracts were dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (3:1 switching to 3:2) to give the title compound as a white solid (0.29g, 50%). LCMS: R_t 3.39 min; *m/z* 574 (MH^+).

Intermediate 10: 4-{(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino)-3-methoxy-3-oxopropyl)phenyl 4-[(2,2-dicyclohexylacetyl)amino]-1-piperidinecarboxylate hydrochloride

To a solution of Intermediate 9 (0.22g) in anhydrous dichloromethane (4ml), under a nitrogen atmosphere, was added Intermediate 58 (0.14g) followed by diisopropylethylamine (0.08ml). After stirring for 4h at 20°C the mixture was diluted with dichloromethane (50ml), washed with saturated aqueous potassium carbonate (3 x 25ml) and 1M hydrochloric acid (40ml), dried over sodium sulphate and evaporated *in vacuo* to give a cream solid. To this was added 4M hydrogen chloride in 1,4-dioxane (3ml) and the mixture was stirred for 3h at 20°C. The solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a cream solid (0.24g, 95%). LCMS: R_t 3.05 min; *m/z* 641 (MH^+).

Intermediate 11: Tert-butyl (2S)-2-[((2S)-2-[[(benzyloxy)carbonyl]amino]-4-methylpentanoyl)amino]-3-(4-hydroxyphenyl)propanoate

To a solution of N-carbobenzyloxy-L-leucine (8.6g) in acetonitrile (150ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.83g) and 1-hydroxybenzotriazole (4.81g). After stirring for 30 mins at 20°C L-tyrosine *tert*-butyl ester (7.7g) was added and stirring was continued for 18h. The mixture was concentrated *in vacuo* to *ca.* 10ml and the residue was partitioned between 1M hydrochloric acid (300ml) and ethyl acetate (150ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (150ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (150ml), water (2 x 150ml) and brine (100ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with chloroform to give the title compound as a white foam (15g, 96%). LCMS: R_t 3.56 min; *m/z* 485 (MH^+).

Intermediate 12: Tert-butyl (2S)-2-[((2S)-2-[[(benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy]phenyl)propanoate

To a solution of Intermediate 11 (1.36g) in dichloromethane (15ml), under a nitrogen atmosphere, was added 4-nitrophenyl chloroformate (0.75g) and 4-dimethylaminopyridine (0.47g). The mixture was stirred for 18h at 20°C then diluted with chloroform (50ml), washed with 1M hydrochloric acid (2 x 30ml) and water (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (4:1 switching to 1:1) to give the title compound as a white solid (1.34g, 74%). LCMS: R_t 3.89 min; *m/z* 650 (MH^+).

Intermediate 13: 4-[(2S)-2-[((2S)-2-[[(Benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-morpholinecarboxylate

To a solution of Intermediate 12 (0.34g) in dichloromethane (8ml), under a nitrogen atmosphere, was added morpholine (0.06ml) and diisopropylethylamine (0.15ml). The mixture was stirred for 18h at 20°C then diluted with chloroform (30ml), washed with saturated aqueous potassium carbonate (3 x 40ml), 2M hydrochloric acid (40ml) and water (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (3:2) to give the title compound as a colourless gum (0.31g, 99%). LCMS: R_t 3.60 min; *m/z* 598 (MH^+).

Intermediate 13 (Alternative procedure): 4-[(2S)-2-[((2S)-2-[[(Benzyloxy) carbonyl]amino]-4-methylpentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-morpholinecarboxylate

To a solution of triphosgene (2.24g) in anhydrous dichloromethane (50ml), under a nitrogen atmosphere, was added a solution of Intermediate 11 (10g) in anhydrous THF (50ml) followed by diisopropylethylamine (3.94ml). After stirring for 4h at 20°C morpholine (2ml) was added followed by diisopropylethylamine (3.94ml). Stirring was continued for 18h then the mixture was partitioned between 1M hydrochloric acid (100ml) and ethyl acetate (75ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (75ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and brine (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with cyclohexane/ethyl acetate (3:1 switching to 1:1) to give the title compound as a white solid (6.8g, 58%).

Intermediate 14: 4-[(2S)-2-[((2S)-2-[[(Benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(aminocarbonyl)-1-piperidinecarboxylate

This was similarly prepared from Intermediate 11 (9g) and isonipecotamide (5.2g). The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate to give the title compound as a white solid (3.52g, 30%).

Intermediate 14: (Alternative Procedure) 4-[(2S)-2-[((2S)-2-[[(Benzyloxy) carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(aminocarbonyl)-1-piperidinecarboxylate

To a solution of Intermediate 12 (1g) in dichloromethane (20ml), under a nitrogen atmosphere, was added isonipecotamide (0.23g) and diisopropylethylamine (0.43ml). The mixture was stirred for 18h at 20°C then diluted with chloroform (80ml), washed with saturated aqueous potassium carbonate (3 x 50ml), 2M hydrochloric acid (50ml) and water (50ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (3:2) switching to ethyl acetate/methanol (4:1) to give the title compound as a white solid (0.46g, 47%). LCMS: R_t 3.47 min; *m/z* 639 (MH^+).

Intermediate 15: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-morpholinecarboxylate

To 10% palladium on carbon, Degussa type E101 (0.09g), under a nitrogen atmosphere, was added a solution of Intermediate 13 (0.3g) in ethanol (20ml) followed by ammonium formate (0.17g). After stirring for 4h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (10ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between dichloromethane (50ml) and 1M sodium hydroxide (15ml). The layers were separated and the organic phase was further washed with 1M sodium hydroxide (15ml) and water (15ml), dried over sodium sulphate and evaporated *in vacuo* to give the title compound as a grey gum (0.1g, 41%). LCMS: R_t 2.43 min; *m/z* 464 (MH^+).

Intermediate 16: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(aminocarbonyl)-1-piperidinecarboxylate

This was similarly prepared from Intermediate 14 (0.46g). The title compound was obtained as a pale yellow gum (0.36g, 99%). LCMS: R_t 2.33 min; *m/z* 505 (MH^+).

Intermediate 17: 4-[(2S)-2-[((2S)-2-[[(Benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-acetyl-1-piperazine carboxylate

To a solution of triphosgene (0.24g) in anhydrous dichloromethane (5ml), under a nitrogen atmosphere, was added a solution of Intermediate 11 (1g) in anhydrous THF (10ml) followed by diisopropylethylamine (0.43ml). After stirring for 4h at 20°C 1-acetylpiperazine (0.32g) was added followed by diisopropylethylamine (0.43ml). Stirring was continued for 18h then the mixture was partitioned between 1M hydrochloric acid (100ml) and ethyl acetate (75ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (75ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and brine (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate switching to ethyl acetate/ethanol (9:1) to give the title compound as a white foam (1.3g, 99%). LCMS: R_t 3.44 min; *m/z* 639 (MH^+).

Intermediate 18: 4-[(2S)-2-[((2S)-2-[[(Benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-benzoyl-1-piperazine carboxylate

To a solution of triphosgene (0.24g) in anhydrous dichloromethane (5ml), under a nitrogen atmosphere, was added a solution of Intermediate 11 (1g) in anhydrous THF (10ml) followed

by diisopropylethylamine (0.43ml). After stirring for 4h at 20°C Intermediate 56 (0.78g) was added followed by diisopropylethylamine (1.15ml). Stirring was continued for 18h then the mixture was partitioned between 1M hydrochloric acid (100ml) and ethyl acetate (75ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (75ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and brine (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:1 switching to 2:1) to give the title compound as a white foam (1.02g, 71%). LCMS: R_t 3.71 min; *m/z* 701 (MH^+).

Intermediate 19: 4-[(2S)-2-[((2S)-2-[[(Benzyloxy)carbonyl]amino]-4-methyl pentanoyl)amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(1-piperidinylcarbonyl)-1-piperidinecarboxylate

This was similarly prepared from Intermediate 11 (1.81g) and Intermediate 55 (0.91g). The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (20:1) to give the title compound as a white foam (1.24g, 47%). LCMS: R_t 3.63 min; *m/z* 707 (MH^+).

Intermediate 20: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino)-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(1-piperidinylcarbonyl)-1-piperidinecarboxylate

To 10% palladium on carbon, Degussa type E101 (0.27g), under a nitrogen atmosphere, was added a solution of Intermediate 19 (1.24g) in ethanol (20ml) followed by ammonium formate (0.77g). After stirring for 4h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (20ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between dichloromethane (50ml) and 1M sodium hydroxide (15ml). The layers were separated and the organic phase was further washed with 1M sodium hydroxide (15ml) and water (15ml), dried over sodium sulphate and evaporated *in vacuo* to give the title compound as a white foam (0.55g, 54%). LCMS: R_t 2.63 min; *m/z* 573 (MH^+).

Intermediate 21: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino)-3-(tert-butoxy)-3-oxopropyl]phenyl 4-acetyl-1-piperazinecarboxylate hydrochloride

To 10% palladium on carbon, Degussa type E101 (0.4g), under a nitrogen atmosphere, was added a solution of Intermediate 17 (1.28g) in ethanol (30ml) followed by ammonium formate (0.38g). After stirring for 6h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (20ml). The combined filtrate and washings

were evaporated *in vacuo* and the residue was partitioned between dichloromethane (70ml) and 1M sodium hydroxide (30ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 x 50ml). The combined organic extracts were dried over sodium sulphate. The solution was treated with 4M hydrogen chloride in 1,4-dioxane (0.55ml) and evaporated *in vacuo* to give the title compound as a white solid (1.02g, 94%). LCMS: R_t 2.46 min; *m/z* 505 (MH^+).

Intermediate 22: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-benzoyl-1-piperazinecarboxylate hydrochloride

To 10% palladium on carbon, Degussa type E101 (0.3g), under a nitrogen atmosphere, was added a solution of Intermediate 18 (1g) in ethanol (30ml) followed by ammonium formate (0.27g). After stirring for 6h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (20ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between dichloromethane (70ml) and 1M sodium hydroxide (30ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 x 50ml). The combined organic extracts were dried over sodium sulphate. The solution was treated with 4M hydrogen chloride in 1,4-dioxane (0.4ml) and evaporated *in vacuo* to give the title compound as a white solid (0.8g, 100%). LCMS: R_t 2.72 min; *m/z* 567 (MH^+).

Intermediate 23: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-morpholinecarboxylate hydrochloride

To 10% palladium on carbon, Degussa type E101 (2.1g), under a nitrogen atmosphere, was added a solution of Intermediate 13 (6.8g) in ethanol (500ml) followed by ammonium formate (4.1g). After stirring for 17h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (50ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between dichloromethane (150ml) and 1M sodium hydroxide (75ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 x 100ml). The combined organic extracts were dried over sodium sulphate. The solution was treated with 1M hydrogen chloride in ether (13ml) and evaporated *in vacuo*. The residue was triturated with ether to give the title compound as a white solid (4.8g, 87%).
LCMS: R_t 2.50 min; *m/z* 464 (MH^+).

Intermediate 24: 4-[(2S)-2-[[(2S)-2-Amino-4-methylpentanoyl]amino]-3-(tert-butoxy)-3-oxopropyl]phenyl 4-(aminocarbonyl)-1-piperidinecarboxylate hydrochloride

To 10% palladium on carbon, Degussa type E101 (1.1g), under a nitrogen atmosphere, was added a solution of Intermediate 14 (3.41g) in ethanol (80ml) followed by ammonium formate (2.1g). After stirring for 3h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (40ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between chloroform (500ml) and saturated aqueous sodium hydrogen carbonate (200ml). The layers were separated and the aqueous phase was further extracted with chloroform (2 x 100ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 x 100ml) and water (2 x 100ml) then dried over sodium sulphate. The solution was treated with 4M hydrogen chloride in 1,4-dioxane (1.5ml) and evaporated *in vacuo*. The residue was azeotroped with toluene (2 x 50ml) to give the title compound as a white solid (2.88g, 100%). LCMS: R_t 2.36 min; *m/z* 505 (MH^+).

Intermediate 25: Tert-butyl (2S)-2-[[(2S)-2-{[2-[2-(tert-butyl)phenoxy]acetyl} amino)-4-methylpentanoyl]amino)-3-(4-hydroxyphenyl)propanoate

To 10% palladium on carbon, Degussa type E101 (0.63g), under a nitrogen atmosphere, was added a solution of Intermediate 11 (2g) in ethanol (20ml) followed by ammonium formate (1.8g). After stirring for 2h at 20°C the mixture was filtered through a pad of Harborlite J2 Filter Aid and the pad was washed with ethanol (50ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between dichloromethane (100ml) and saturated aqueous sodium hydrogen carbonate (50ml). The layers were separated and the organic phase was further washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white solid. A solution of this in DMF (5ml) was added to a pre-mixed solution of Intermediate 46 (0.879g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.809g) and 1-hydroxybenzotriazole (0.578g) in acetonitrile (10ml) which had been stirring under a nitrogen atmosphere for 30 mins at 20°C. Stirring was continued for 18h. The mixture was diluted with ethyl acetate (200ml), washed with 1M hydrochloric acid (3 x 50ml), saturated aqueous sodium hydrogen carbonate (3 x 50ml) and brine (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give the title compound as a white foam (2.1g, 94%). LCMS: R_t 3.83 min; *m/z* 541 (MH^+).

Intermediate 26: Tert-butyl (2S)-2-[[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl} amino)-4-methylpentanoyl]amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy)phenyl) propanoate

To a solution of Intermediate 25 (2.1g) in dichloromethane (20ml), under a nitrogen atmosphere, was added 4-nitrophenyl chloroformate (1.1g) and 4-dimethylaminopyridine (0.69g). The mixture was stirred for 18h at 20°C then diluted with chloroform (80ml), washed with 1M hydrochloric acid (2 x 50ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with cyclohexane/ethyl acetate (2:1) to give the title compound as a clear oil (2.65g, 97%). LCMS: R_t 4.17 min; *m/z* 706 (MH^+).

Intermediate 27: 4-[(2S)-2-{{(2S)-2-[(2-Bromoacetyl)amino]-4-methylpentanoyl} amino)-3-(tert-butoxy)-3-oxopropyl]phenyl 4-morpholinecarboxylate

A solution of Intermediate 23 (0.5g) and diisopropylethylamine (0.19ml) in dichloromethane (10ml) was cooled to 0-5°C. To this was added bromoacetyl chloride (0.09ml) followed by diisopropylethylamine (0.19ml) and stirring was continued for 2h. The mixture was diluted with dichloromethane (50ml), washed with 2M hydrochloric acid (50ml), saturated aqueous sodium hydrogen carbonate (50ml) and brine (30ml), dried over magnesium sulphate and evaporated *in vacuo* to give the title compound as a white foam (0.52g, 89%).
LCMS: R_t 3.28 min; *m/z* 584 (MH^+).

Intermediate 28: 4-[(2S)-2-{{(2S)-2-[(2-Bromoacetyl)amino]-4-methylpentanoyl} amino)-3-methoxy-3-oxopropyl]phenyl 4-[(2-phenylacetyl)amino]-1-piperidine carboxylate

To a solution of Intermediate 8 (0.48g) in anhydrous dichloromethane (4ml) was added diisopropylethylamine (0.142ml). The mixture was cooled to 0-5°C and bromoacetyl chloride (0.07ml) was added. Stirring was continued for 1h allowing the reaction to warm to 20°C. The mixture was diluted with dichloromethane (5ml) and washed with saturated aqueous sodium hydrogen carbonate (5ml), water (10ml) and brine (10ml), dried over sodium sulphate and evaporated *in vacuo* to give the title compound as a white solid (0.464g, 85%).
LCMS: R_t 3.20 min; *m/z* 672 $[M-H]^-$.

Intermediate 29: (2S)-3-[4-(Allyloxy)phenyl]-2-[[(9H-fluoren-9-ylmethoxy) carbonyl]amino}propanoic acid bound to Wang resin via acid

To Wang resin (100-200 mesh, 10g) was added a solution of (2S)-3-[4-(allyloxy)phenyl]-2-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propanoic acid (8.5g) in DMF (45ml). After 15 mins pyridine (2.4ml) was added followed by 2,6-dichlorobenzoyl chloride (2.75ml). The

mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 40ml), dichloromethane (5 x 40ml) and ether (5 x 40ml) then dried *in vacuo*. The amount of (2S)-3-[4-(allyloxy)phenyl]-2-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino} propanoic acid substituted on the resin was calculated to be 0.52 mmol/g.

Intermediate 30: (2S)-3-[4-(Allyloxy)phenyl]-2-[{(2S)-2-[[(9H-fluoren-9-ylmethoxy) carbonyl]amino)-4-methylpentanoyl)amino]propanoic acid bound to Wang resin via acid

Intermediate 29 (2.5mmol) was treated with 20% piperidine in DMF (15ml) and shaken for 1h 30mins at 20°C. The resin was filtered and washed with DMF (5 x 20ml). A solution of Fmoc-leucine (2.8g) in DMF (10ml) was added followed by a solution of benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluoro phosphate (4.1g) in DMF (5ml) and diisopropylethylamine (2.8ml). The mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 20ml), dichloromethane (5 x 20ml) and ether (5 x 20ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 4.22 min; *m/z* 557 (MH^+).

Intermediate 31: (2S)-3-[4-(Allyloxy)phenyl]-2-[[(2S)-2-({2-[2-(tert-butyl)phenoxy] acetyl}amino)-4-methylpentanoyl]amino}propanoic acid bound to Wang resin via acid

Intermediate 30 (1mmol) was treated with 20% piperidine in DMF (10ml) and shaken for 1h at 20°C. The resin was filtered and washed with DMF (5 x 10ml). A solution of Intermediate 46 (0.314g) in DMF (10ml) was added followed by a solution of benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluoro phosphate (0.78g) in DMF (5ml) and diisopropylethylamine (0.68ml). The mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 10ml), dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 4.27 min; *m/z* 525 (MH^+).

Intermediate 32: (2S)-3-[4-(Allyloxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methyl phenoxy)acetyl]amino}pentanoyl)amino]propanoic acid bound to Wang resin via acid

This was similarly prepared from Intermediate 30 (0.97mmol) and (2-methylphenoxy)acetic acid (0.48g). LCMS: R_t 3.89 min; *m/z* 483 (MH^+).

Intermediate 33: (2S)-2-[[(2S)-2-([2-[2-(Tert-butyl)phenoxy]acetyl)amino)-4-methylpentanoyl]amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy}phenyl)propanoic acid bound to Wang resin via acid

Intermediate 31 (1mmol) was treated with a solution of phenylsilane (1ml) in dichloromethane (9ml) followed by tetrakis(triphenylphosphine)palladium(0) (0.1g). The mixture was shaken for 40 mins at 20°C. The resin was filtered and washed with dichloromethane (5 x 10ml) then retreated with a solution of phenylsilane (1ml) in dichloromethane (9ml) followed by tetrakis(triphenylphosphine)palladium(0) (0.1g). After shaking for 40 mins at 20°C the resin was filtered and washed with dichloromethane (5 x 10ml) then treated with a solution of diisopropylethylamine (1.74ml) in 1:1 dichloromethane/THF (16ml). 4-Nitrophenyl chloroformate (2g) was added portionwise and the mixture was shaken for 18h at 20°C. The resin was filtered and washed with dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 4.33 min; *m/z* 650 (MH^+).

Intermediate 34: (2S)-2-[((2S)-4-Methyl-2-[[2-(2-methylphenoxy)acetyl]amino) pentanoyl)amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy)phenyl)propanoic acid bound to Wang resin via acid

This was similarly prepared from Intermediate 32 (0.97mmol). LCMS: R_t 3.31 min; *m/z* 443 (MH^+).

Intermediate 35: (2S)-2-[((2S)-2-[(9H-Fluoren-9-ylmethoxy)carbonyl]amino)-4-methylpentanoyl)amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy}phenyl)propanoic acid bound to Wang resin via acid

This was similarly prepared from Intermediate 30 (1.05mmol). LCMS: R_t 4.32 min; *m/z* 682 (MH^+).

Intermediate 36: (2S)-2-[((2S)-2-[(9H-Fluoren-9-ylmethoxy)carbonyl]amino)-4-methylpentanoyl)amino]-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid bound to Wang resin via acid

Intermediate 35 (1.05mmol) was treated with a solution of 1-(2-furoyl)piperazine (0.57g) in 1:1 dichloromethane/THF (9ml) followed by diisopropylethylamine (1.1ml). After shaking for 4h at 20°C the resin was filtered and washed with dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/

dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 3.67 min; *m/z* 723 (MH^+).

Intermediate 37: (2S)-3-(4-[[(4-[[2-(4-Chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy}phenyl)-2-[((2S)-2-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino)-4-methylpentanoyl)amino]propanoic acid bound to Wang resin via acid

This was similarly prepared from Intermediate 35 (1.7mmol) and Intermediate 53 (1.02g). LCMS: R_t 4.03 min; *m/z* 795 (MH^+).

Intermediate 38: (2S)-2-(((2S)-2-[(2-Bromoacetyl)amino]-4-methylpentanoyl) amino)-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl]propanoic acid bound to Wang resin via acid

Intermediate 36 (1.05mmol) was treated with 20% piperidine in DMF (8ml) and shaken for 1h 30mins at 20°C. The resin was filtered and washed with DMF (5 x 10ml). A solution of bromoacetic acid (0.44g) in DMF (8ml) was added followed by 1,3-diisopropylcarbodiimide (0.49ml). The mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 10ml), dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 3.11 min; *m/z* 621 (MH^+).

Intermediate 39: (2S)-2-(((2S)-2-[(2-Bromoacetyl)amino]-4-methylpentanoyl) amino)-3-(4-{[(4-[[2-(4-chlorophenyl)acetyl]amino)-1-piperidinyl)carbonyl]oxy} phenyl)propanoic acid bound to Wang resin via acid

This was similarly prepared from Intermediate 37 (0.73mmol). LCMS: R_t 3.43 min; *m/z* 695 (MH^+).

Intermediate 40: (2S)-3-[4-(Allyloxy)phenyl]-2-(((2S)-2-[(2-bromoacetyl)amino]-4-methylpentanoyl)amino)propanoic acid bound to Wang resin via acid

Intermediate 30 (0.55mmol) was treated with 20% piperidine in DMF (6ml) and shaken for 1h at 20°C. The resin was filtered and washed with DMF (5 x 10ml). A solution of bromoacetic acid (0.23g) in DMF (3ml) was added followed by 1,3-diisopropylcarbodiimide (0.26ml). The mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 10ml), dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 3.47 min; *m/z* 455 (MH^+).

Intermediate 41: (2S)-3-[4-(Allyloxy)phenyl]-2-[((2S)-2-[[2-(2-cyclohexylphenoxy) acetyl]amino]-4-methylpentanoyl)amino]propanoic acid bound to Wang resin via acid

Intermediate 40 (0.55mmol) was treated with DMF (4ml). 2-Cyclohexylphenol (0.97g), potassium carbonate (0.76g) and sodium iodide (0.82g) were added and the mixture was shaken for 40h at 20°C. The resin was filtered and washed with water (3 x 5ml), DMF (5 x 5ml), dichloromethane (5 x 5ml) and ether (5 x 5ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 4.49 min; *m/z* 551 (MH^+).

Intermediate 42: (2S)-2-[((2S)-2-[[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methylpentanoyl)amino]-3-(4-[[(4-nitrophenoxy)carbonyl]oxy}phenyl)propanoic acid bound to Wang resin via acid

Intermediate 41 (0.55mmol) was treated with a solution of phenylsilane (1.35ml) in dichloromethane (10ml) followed by tetrakis(triphenylphosphine)palladium(0) (0.063g). The mixture was shaken for 40 mins at 20°C. The resin was filtered and washed with dichloromethane (5 x 10ml) then retreated with a solution of phenylsilane (1.35ml) in dichloromethane (10ml) followed by tetrakis(triphenylphosphine)palladium(0) (0.063g). After shaking for 40 mins at 20°C the resin was filtered and washed with dichloromethane (5 x 10ml) then treated with a solution of diisopropylethylamine (1.9ml) in 1:1 dichloromethane/THF (8ml). 4-Nitrophenyl chloroformate (2.2g) was added portionwise and the mixture was shaken for 18h at 20°C. The resin was filtered and washed with dichloromethane (5 x 10ml) and ether (5 x 10ml) then dried *in vacuo*. A 5mg sample was treated with trifluoroacetic acid/ dichloromethane (1:1) (1ml) for 0.5h at 20°C, resin was filtered and the filtrate analysed by LCMS: R_t 4.54 min; *m/z* 676 (MH^+).

Intermediate 43: (2-Iodophenoxy)acetic acid

tert-Butyl bromoacetate (4.0ml) was added to a suspension containing 2-iodophenol (4.98g) and potassium carbonate (6.3g) in DMF (40ml). The mixture was stirred for 1h at 20°C under a nitrogen atmosphere and was then partitioned between ethyl acetate (150ml) and water (100ml). The aqueous layer was extracted with fresh ethyl acetate (2 x 80ml) and the combined organic extracts washed with brine (100ml), dried over magnesium sulphate and evaporated *in vacuo* to give a clear liquid (7.56g). This was dissolved in dichloromethane (20ml) and trifluoroacetic acid (8ml) and the solution stirred for 2h at 20°C. Solvent was evaporated *in vacuo* and the residue triturated in a mixture of cyclohexane/ethyl acetate

(5:1) to give the title compound as a white solid (5.19g, 82%). LCMS: R_t 3.02 min; *m/z* 277 $[M-H]^-$.

Intermediate 44: {[3-(1-Piperidinylcarbonyl)-2-naphthyl]oxy}acetic acid

This was similarly prepared from 3-(1-piperidinylcarbonyl)-2-naphthol (Griffiths and Hawkins, 1977)((4.98g). The intermediate ester was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) and the title compound was isolated as a white solid (3.2g, 53%). LCMS: R_t 3.74 min; *m/z* 314 (MH^+).

Intermediate 45: Dibenzo[b,d]furan-4-carboxylic acid

A solution of 1.6M *n*-butyllithium in hexane (18.5ml) was added dropwise to a stirred solution of dibenzofuran (5.0g) in anhydrous THF (25ml) at -78°C under a nitrogen atmosphere. The resulting suspension was allowed to warm to 20°C where it was stirred for 3h. It was then cooled to -78°C and added to a mixture of excess solid carbon dioxide in diethyl ether (250ml) under a nitrogen atmosphere. The resulting white suspension was allowed to stand for 1h at 20°C and was then diluted with 2M sodium hydroxide (500ml). The aqueous extract was washed with ether (3 x 200ml), acidified to pH 1 with 6M hydrochloric acid and extracted with ethyl acetate (3 x 200ml). The combined organic extracts were washed with brine (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give the title compound as a white solid (3.64g, 58%). LCMS: R_t 5.06 min; *m/z* 213 (MH^+).

Intermediate 46: [2-(Tert-butyl)phenoxy]acetic acid

Methyl bromoacetate (3.0ml) was added to a suspension containing 2-*tert*-butylphenol (5.0ml) and potassium carbonate (10.6g) in DMF (250ml). The mixture was stirred for 20h at 20°C under a nitrogen atmosphere and was then evaporated *in vacuo* to a slurry which was partitioned between ether (200ml) and 1M hydrochloric acid (100ml). The aqueous layer was extracted with more ether (100ml) and the combined organic extracts washed with brine (100ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:9) to give a clear liquid (6.64g). This was dissolved in methanol (100ml) and 2M sodium hydroxide (100ml) and the solution was stirred for 0.5h at 20°C. The methanol was evaporated *in vacuo* and the aqueous residue was washed with diethyl ether (50ml), acidified to pH 1 with 6M hydrochloric acid and extracted with ethyl acetate (2 x 200ml). The combined organic extracts were washed with brine (50ml), dried over magnesium sulphate

and evaporated *in vacuo* to give the title compound as a white crystalline mass (5.86g, 95%). LCMS: R_t 3.78 min; *m/z* 207 [M-H]$^-$.

Intermediate 47: 4-(2-Methoxy-2-oxoethoxy)benzoic acid

Methyl bromoacetate (1.6ml) was added to a suspension containing tert-butyl 4-hydroxybenzoate (Shah *et al.*, 1992) (3.03g), sodium iodide (2.55g) and potassium carbonate (4.2g) in acetonitrile (60ml). The mixture was stirred for 17h at 90°C under a nitrogen atmosphere and then allowed to cool to 20°C. It was then partitioned between water (50ml) and ethyl acetate (100ml) and the organic extract washed with water (2 x 80ml) and brine (60ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with a gradient of ethyl acetate/petroleum ether (1:9) to ethyl acetate/petroleum ether (1:2) to give a pale red gum (3.85g). This was dissolved in dichloromethane (50ml) and trifluoroacetic acid (15ml) was added and the solution was stirred for 3h at 20°C. Solvents were evaporated *in vacuo* to give the title compound as a white solid (2.97g, 91%). LCMS: R_t 2.45 min; *m/z* 211 (MH$^+$).

Intermediate 48: [4-(1-Piperidinylcarbonyl)phenoxy]acetic acid

To a suspension of Intermediate 47 (2.95g) in acetonitrile (55ml) was added diisopropylethylamine (3.5ml) followed by (1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (4.5g). The resulting solution was stirred for 10mins at 20°C under a nitrogen atmosphere and then piperidine (1.4ml) was added and the mixture was stirred for 18h at 20°C under a nitrogen atmosphere and then evaporated *in vacuo*. The residue was partitioned between ethyl acetate (100ml) and 8% aqueous sodium hydrogen carbonate (65ml) and the organic extract was washed with 2M hydrochloric acid (50ml) and brine (100ml), dried over magnesium sulphate and evaporated *in vacuo* to give an orange oil (4.05g). This was dissolved in methanol (100ml) and 1M sodium hydroxide (30ml) was added and the mixture stirred for 3h at 20°C. It was then acidified to pH 1 with 1M hydrochloric acid and cooled to 5°C and the precipitate collected by filtration and dried *in vacuo* to give the title compound as a white solid (3.03g, 80%). LCMS: R_t 4.17 min; *m/z* 264 (MH$^+$).

Intermediate 49: (2-Benzoylphenoxy)acetic acid

Methyl bromoacetate (3.0ml) was added to a suspension containing 2-hydroxybenzophenone (2.3g), potassium carbonate (3.2g) and sodium iodide (2.33g) in acetonitrile (35ml). The mixture was stirred for 18h at 90°C under a nitrogen atmosphere and

was then allowed to cool to 20°C. It was then partitioned between ethyl acetate (80ml) and water (60ml) and the organic extract washed with water (2 x 60ml) and brine (60ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:1) to give a pale yellow oil (3.05g). This was dissolved in methanol (100ml) and 1M sodium hydroxide (35ml) and the solution was stirred for 18h at 20°C. The solution was acidified to pH 1 with 2M hydrochloric acid and extracted with ethyl acetate (2 x 80ml). The combined organic extracts were washed with water (2 x 70ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with a gradient of ethyl acetate/petroleum ether (1:1) to ethyl acetate/methanol (4:1) to give the title compound as a pale yellow gum (1.62g, 57%). LCMS: R_t 3.41 min; *m/z* 257 (MH$^+$).

Intermediate 50: [(1-Bromo-2-naphthyl)oxy]acetic acid

This was similarly prepared from 1-bromo-2-naphthol (10.55g). The intermediate ester was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:3) and the title compound was isolated as a pale brown solid (11.36g, 89%). LCMS: R_t 4.17 min; *m/z* 281 [M-H]$^-$.

Intermediate 51: [4-(Aminocarbonyl)phenoxy]acetic acid

A solution of 4-formylphenoxyacetic acid (1.86g) and hydroxylamine hydrochloride (1.07g) in 98% formic acid (50ml) was stirred under reflux for 2h and then cooled in an ice bath. The precipitate was collected by filtration, washed with water and dried *in vacuo* to give a white solid (1.1g). A mixture of this with powdered potassium hydroxide (2.3g) in *tert*-butanol (50ml) was stirred under reflux under a nitrogen atmosphere for 4h and then allowed to cool. The mixture was diluted with water (100ml), washed with ethyl acetate (50ml) and acidified to pH 2 with 6M hydrochloric acid. The precipitate was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a white solid (1.06g, 53%). LCMS: R_t 1.90 min; *m/z* 196 (MH$^+$).

Intermediate 52: Tert-butyl 4-amino-1-piperidinecarboxylate

Sodium triacetoxyborohydride (30.2g) was added portionwise over 10min to an ice-cooled mixture of 1-(*tert*-butoxycarbonyl)-4-piperidone (20.07g), dibenzylamine (19.7g) and acetic acid (5ml) in dichloromethane (500ml) and stirring was then continued for 16h at 20°C. The solution was then treated cautiously with 2M sodium hydroxide (400ml) and the separated

organic layer, dried over magnesium sulphate and evaporated *in vacuo*. The residue was triturated in hexane/ether (2:1) (250ml) to give a white solid (18.75g). This was dissolved in a mixture of THF (50ml), ethanol (50ml) and 2M hydrochloric acid (8ml) and the solution added to a suspension of 20% palladium hydroxide on carbon (5.0g) in ethanol (100ml). The mixture was hydrogenated at 20°C and 1 atmosphere for 17h and was then filtered through a pad of Harborlite J2 Filter Aid and the pad washed with ethanol (100ml). The combined filtrate and washings were evaporated *in vacuo* and the residue dissolved in water (50ml) and adjusted to pH 9 with 2M sodium hydroxide and evaporated *in vacuo*. The residue was leached into a mixture of ethanol (30ml) and chloroform (70ml) and insoluble material removed by filtration. The mother liquors were evaporated *in vacuo* to give the title compound as a colourless oil (10.04g, 49%). LCMS: R_t 1.81 min; *m/z* 201 (MH^+).

Intermediate 53: 2-(4-Chlorophenyl)-N-(4-piperidinyl)acetamide hydrochloride

To a solution of 4-chlorophenylacetic acid (2.55g) in acetonitrile (100ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.16g) and 1-hydroxybenzotriazole (2.22g). After stirring for 10 mins at 20°C a solution of Intermediate 52 (3g) in acetonitrile (20ml) was added, and stirring was continued for 18h. The mixture was evaporated *in vacuo* and the residue partitioned between water (100ml) and ethyl acetate (100ml). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 x 80ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give a pale yellow solid. This was triturated with ether to give a white solid (4.15g). A portion of this (2.36g) was dissolved in 1,4-dioxane (100ml) and 4M hydrogen chloride in 1,4-dioxane (12ml) was added. The solution was stirred for 18h at 20°C and then a further portion of 4M hydrogen chloride in 1,4-dioxan (8ml) was added. Stirring was continued for a further 18h at 20°C and the solution was evaporated *in vacuo* to give a white solid. This was triturated in ether to give the title compound as a white solid (1.9g, 77%). LCMS: R_t 1.89 min; *m/z* 253 (MH^+).

Intermediate 54: N-(4-Fluorobenzyl)-4-piperidinecarboxamide hydrochloride

To a solution of 1-*tert*-butoxycarbonylpiperidine-4-carboxylic acid (3.61g) in acetonitrile (25ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.21g) and 1-hydroxybenzotriazole (2.29g). After stirring for 20 mins at 20°C 4-fluorobenzylamine (2.0ml) was added and stirring was continued for 3h. The mixture was concentrated *in vacuo* and the residue was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (200ml). The layers were separated and the

organic phase was washed with 1M hydrochloric acid (3 x 50ml), saturated aqueous sodium hydrogen carbonate (3 x 50ml) and brine (50ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with a gradient of cyclohexane/ethyl acetate (1:1) to neat ethyl acetate to give colourless crystals (5.02g). A portion of this (4.98g) was dissolved in 1,4-dioxane (20ml) and 4M hydrogen chloride in 1,4-dioxane (15ml) was added. The mixture was stirred for 2h at 20°C and the precipitate was collected by filtration, washed with 1,4-dioxane and diethyl ether and dried *in vacuo* to give the title compound as a white hygroscopic solid (3.54g, 83%). LCMS: R_t 1.52 min; *m/z* 237 (MH^+).

Intermediate 55: 1-(4-Piperidinylcarbonyl)piperidine hydrochloride

This was similarly prepared from 1-*tert*-butoxycarbonylpiperidine-4-carboxylic acid (3.68g) and piperidine (1.6ml). The intermediate amide was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (10:1) and the title compound was isolated as a white solid (3.26g, 93%). MS: *m/z* 197 (MH^+), TLC: R_f 0.1 [dichloromethane/ethanol/880 ammonia (50:8:1) visualisation with iodoplatinic acid].

Intermediate 56: 1-Benzoylpiperazine

This was similarly prepared from benzoic acid (5.02g) and 1-(*tert*-butoxycarbonyl)piperazine (7.66g) and the title compound was isolated as a white solid (7.7g, 82%). LCMS: R_t 0.51 min; *m/z* 191(MH^+).

Intermediate 57: 2-Cyclohexyl-N-(4-piperidinyl)acetamide

A solution of 4-amino-1-benzylpiperidine (5.0ml), cyclohexaneacetic acid (3.79g) and (1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (8.35g) in acetonitrile (60ml) was stirred for 18h at 20°C under a nitrogen atmosphere and was then evaporated *in vacuo* to a syrup. This was partitioned between ethyl acetate (200ml) and saturated aqueous sodium hydrogen carbonate (200ml). The organic extract was washed with saturated aqueous sodium hydrogen carbonate (2 x 100ml) and brine (100ml), dried over magnesium sulphate and evaporated *in vacuo* to give an off-white solid. This was crystallised from cyclohexane to give cream crystals (6.24g). A portion of this (3.8g) was dissolved in ethanol (100ml) and treated with 10% palladium on carbon, Degussa type E101 (1.2g) and ammonium formate (2.24g). The mixture was stirred for 2.5h at 20°C under a nitrogen atmosphere and was then filtered through a pad of Harborlite J2 Filter Aid and the pad washed with ethanol (100ml). The combined filtrate and washings were evaporated *in vacuo*

and the residue was partitioned between chloroform (100ml) and 0.5M potassium hydroxide (10ml). The layers were separated and the aqueous phase extracted with fresh chloroform (2 x 100ml) and the combined organic extracts dried over magnesium sulphate and evaporated *in vacuo* to give a white solid. This was triturated with ether to give the title compound as a white solid (2.01g, 60%).
LCMS: R_t 1.93 min; *m/z* 225 (MH^+).

Intermediate 58: 2,2-Dicyclohexyl-N-(4-piperidinyl)acetamide

A solution containing dicyclohexylacetic acid (4.75g), diisopropylethylamine (7.5ml) and benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluoro phosphate (11g) in DMF (250ml) was stirred for 10min at 20°C and then 4-amino-1-benzylpiperidine (4.3ml) was added dropwise over 10min. The mixture was stirred for 18h at 20°C and was then diluted with ethyl acetate (200ml) and the precipitate collected by filtration, washed with ethyl acetate (60ml) and water (50ml) and dried *in vacuo* to give a white solid (5.91g). A portion of this (3g) was suspended in ethanol (300ml) and treated with 10% palladium on carbon, Degussa type E101 (1.2g) and ammonium formate (2.68g). The mixture was stirred for 4h at 20°C under a nitrogen atmosphere and was then filtered through a pad of Harborlite J2 Filter Aid and the pad washed with ethanol (50ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between chloroform (200ml) and 0.5M sodium hydroxide (150ml). The layers were separated and the aqueous phase extracted with fresh chloroform (100ml) and the combined organic extracts dried over magnesium sulphate and evaporated *in vacuo* to give a white solid. This was triturated with ice-cold ether to give the title compound as a white solid (1.8, 78%). LCMS: R_t 2.69 min; *m/z* 307 (MH^+).

Intermediate 59: 2-Phenyl-N-(4-piperidinyl)acetamide

To a solution of phenylacetic acid (3.4g) in acetonitrile (100ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.28g) and 1-hydroxybenzotriazole (3.72g). After stirring for 30 mins at 20°C 4-amino-1-benzylpiperidine (5.1ml) was added and stirring was continued for 18h. The mixture was concentrated *in vacuo* and the residue was partitioned between 2M hydrochloric acid (100ml) and ethyl acetate (75ml). The layers were separated and the aqueous phase was washed with more ethyl acetate (75ml), basified with solid potassium carbonate and extracted with dichloromethane (2 x 100ml). The combined organic extracts were washed with water (2 x 100ml) and brine (50ml), dried over sodium sulphate and evaporated *in vacuo* to give a white solid (4.8g). A portion of this (4.7g) was dissolved in ethanol (150ml) and treated with 10% palladium on carbon, Degussa type E101 (1.5g) and ammonium formate (2.88g). The mixture was stirred for 4h at 20°C under a nitrogen atmosphere and was then filtered through a pad of Harborlite J2 Filter Aid and the pad washed with ethanol (150ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was partitioned between chloroform (100ml) and 0.5M sodium hydroxide (50ml). The layers were separated and the aqueous phase extracted with fresh chloroform (2 x 100ml) and the combined organic extracts dried over sodium sulphate and evaporated *in vacuo* to give the title compound as a white solid (2.4g, 45%). MS: *m/z* 219 (MH^+), TLC: R_f 0.16 [dichloromethane/methanol/880 ammonia (40:10:1) visualisation with iodine].

Examples

Example 1: (2S)-2-[((2S)-2-{[2-(2-Benzoylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid

To a solution of 2-hydroxybenzophenone (0.134g) in anhydrous DMF (0.5ml) was added anhydrous potassium carbonate (0.093g) followed by Intermediate 28 (0.152g) and sodium iodide (0.1g). After stirring for 18h at 20°C the mixture was partitioned between saturated aqueous sodium hydrogen carbonate (10ml) and ethyl acetate (10ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3 x 10ml). The combined organic extracts were washed with water (20ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (10:1) to give a pale yellow solid. To a solution of this in methanol (0.5ml) was added 1M sodium hydroxide (0.22ml). After stirring for 1.5h at 20°C the mixture was partitioned between 2M hydrochloric acid (5ml) and dichloromethane (10ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 x 10ml). The combined organic extracts were washed with water (20ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo* to give the title compound as a pale yellow foam (0.123g, 73%). LCMS: R_t 3.84 min; *m/z* 775 $[M-H]^-$.

Example 2: (2S)-2-({(2S)-4-Methyl-2-[(2-{[3-(1-piperidinylcarbonyl)-2-naphthyl] oxy}acetyl)amino]pentanoyl}amino)-3-{4-[((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl)oxy]phenyl}propanoic acid

To a solution of triphosgene (0.04g) in anhydrous dichloromethane (1ml), under a nitrogen atmosphere, was added a solution of Intermediate 3 (0.2g) in anhydrous THF (2ml) followed

by diisopropylethylamine (0.07ml). After stirring for 3h at 20°C Intermediate 59 (0.09g) was added followed by diisopropylethylamine (0.07ml). Stirring was continued for 18h then the mixture was partitioned between 2M hydrochloric acid (30ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (20ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate switching to ethyl acetate/ethanol (9:1) to give a white foam (0.19g). To a solution of this (0.15g) in methanol (2ml) was added 2M sodium hydroxide (0.18ml). After stirring for 1h at 20°C the mixture was partitioned between 2M hydrochloric acid (40ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:1) to give the title compound as a white solid (0.12g, 54% from Intermediate 3). LCMS: R_t 3.73 min; *m/z* 634 (MH^+).

Example 3: (2S)-3-[4-[((4-[(2,2-Dicyclohexylacetyl)amino]-1-piperidinyl)carbonyl) oxy]phenyl]-2-[[(2S)-4-methyl-2-({2-[4-(1-piperidin;1carbonyl)phenoxy]acetyl} amino)pentanoyl]amino]propanoic acid

To a solution of Intermediate 48 (0.05g) in anhydrous DMF (3ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.04g) and 1-hydroxybenzotriazole (0.03g). After stirring for 30 mins at 20°C Intermediate 10 (0.13g) was added followed by diisopropylethylamine (0.08ml), and stirring was continued for 18h. The mixture was partitioned between 2M hydrochloric acid (40ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (30ml), water (2 x 30ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo* to give a cream coloured solid (0.16g). To a solution of this (0.15g) in methanol (2ml) was added 2M sodium hydroxide (0.18ml). After stirring for 1h at 20°C the mixture was partitioned between 2M hydrochloric acid (40ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting

with chloroform/methanol/acetic acid (95:5:1) to give the title compound as a white solid (0.12g, 62% from Intermediate 10). LCMS: R_t 4.26 min; *m/z* 872 (MH^+).

Example 4: (2S)-2-[[(2S)-4-Methyl-2-({2-[4-(1-piperidinylcarbonyl)phenoxy] acetyl}amino)pentanoyl]amino]-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl] propanoic acid

To a solution of Intermediate 48 (0.06g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.06g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate 15 (0.1g) was added, and stirring was continued for 18h. The mixture was partitioned between water (20ml) and ethyl acetate (25ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (20ml). The combined organic extracts were washed with water (20ml) and brine (20ml), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with dichloromethane/ethanol/880 ammonia (250:8:1) to give a white sticky solid (0.1g). To this was added trifluoroacetic acid (3ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.06g, 50%). LCMS: R_t 3.21 min; *m/z* 653 (MH^+).

Example 5: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[[(2S)-4-methyl-2-({2-[4-(1-piperidinylcarbonyl)phenoxy]acetyl}amino)pentanoyl] amino}propanoic acid

This was similarly prepared from Intermediate 48 (0.06g) and Intermediate 16 (0.12g). The crude intermediate ester was purified by flash column chromatography on silica gel eluting with dichloromethane/ethanol/880 ammonia (500:8:1 switching *via* 250:8:1 to 100:8:1). The title compound was obtained as a white solid (0.09g, 59%). LCMS: R_t 2.84 min; *m/z* 694 (MH^+).

Example 6: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-2-[[2-(2-benzoylphenoxy)acetyl]amino]-4-methylpentanoyl)amino] propanoic acid

This was similarly prepared from Intermediate 49 (0.07g) and Intermediate 16 (0.11g). The crude intermediate ester was purified by flash column chromatography on silica gel eluting with dichloromethane/ethanol/880 ammonia (500:8:1 switching *via* 250:8:1 to 100:8:1). The title compound was obtained as a white solid (0.08g, 42%). LCMS: R_t 3.16 min; *m/z* 687 (MH^+).

Example 7: (2S)-2-[((2S)-2-({2-[4-(Aminocarbonyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid

This was similarly prepared from intermediate 51 (0.06g) and intermediate 16 (0.11g). The crude intermediate ester was purified by flash column chromatography on silica gel eluting with dichloromethane/ethanol/880 ammonia (500:8:1 switching *via* 250:8:1 and 100:8:1 to 75:8:1). The title compound was obtained as a white solid (0.07g, 55%). LCMS: R_t 2.65 min; *m/z* 626 (MH^+).

Example 8: (2S)-3-{4-[({4-[(2-Cyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-[((2S)-2-{[2-(2-iodophenoxy)acetyl]amino}-4-methylpentanoyl) amino]propanoic acid

To a solution of triphosgene (0.058g) in anhydrous dichloromethane (2ml), under a nitrogen atmosphere, was added a solution of Intermediate 4 (0.246g) in anhydrous THF (2ml) followed by diisopropylethylamine (0.11ml). After stirring for 4h at 20°C Intermediate 57 (0.1g) was added followed by diisopropylethylamine (0.07ml). Stirring was continued for 18h then the mixture was partitioned between 2M hydrochloric acid (50ml) and dichloromethane (50ml). The layers were separated and the organic extract was washed with water (20ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give a white foam (0.13g). To a solution of this (0.12g) in methanol (3ml) was added 2M sodium hydroxide (1ml) and water (2ml). After stirring for 18h at 20°C the mixture was partitioned between 2M hydrochloric acid (30ml) and chloroform (30ml). The layers were separated and the organic phase was washed with water (20ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (4:1) to give the title compound as a white solid (0.064g, 20%). LCMS: R_t 4.12 min; *m/z* 805 (MH^+).

Example 9: (2S)-3-{4-[({4-[(2,2-Dicyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-[((2S)-2-{[2-(2-iodophenoxy)acetyl]amino}-4-methylpentanoyl) amino]propanoic acid

This was similarly prepared from Intermediate 4 (0.203g) and Intermediate 58 (0.14g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (9:1) to give the title compound as a white foam (0.153g, 52%). LCMS: R_t 4.45 min; *m/z* 887 (MH^+).

Example 10: (2S)-2-(((2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl]propanoic acid

To a solution of Intermediate 6 (0.165g) in dichloromethane (5ml), under a nitrogen atmosphere, was added morpholine (0.04ml) and diisopropylethylamine (0.05ml). After stirring for 30 mins at 20°C the solution was diluted with dichloromethane (50ml) and washed with saturated aqueous potassium carbonate (3 x 30ml), 1M hydrochloric acid (2 x 40ml) and water (30ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white foam (0.143g). To a solution of this (0.14g) in methanol (2ml) was added 1M sodium hydroxide (2ml) and the mixture was stirred for 30 mins at 20°C, then partitioned between 1M hydrochloric acid (40ml) and ethyl acetate (50ml). The organic extract was washed with brine (30ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (4:1) to give the title compound as a white solid (0.1g, 69%). LCMS: R_t 3.85 min; *m/z* 602 (MH^+).

Example 11: (2S)-2-({(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid

To a solution of Intermediate 6 (0.13g) in dichloromethane (5ml), under a nitrogen atmosphere, was added 1-(2-furoyl)piperazine (0.04g) and diisopropylethylamine (0.04ml). After stirring for 3h at 20°C the solution was diluted with dichloromethane (20ml) and washed with saturated aqueous potassium carbonate (3 x 20ml), 1M hydrochloric acid (2 x 20ml) and water (20ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white foam (0.153g). To a solution of this (0.15g) in methanol (2ml) was added 1M sodium hydroxide (2ml) and the mixture was stirred for 30 mins at 20°C, then partitioned between 1M hydrochloric acid (20ml) and ethyl acetate (20ml). The organic extract was washed with brine (20ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (4:1) to give the title compound as a white solid (0.126g, 92%). LCMS: R_t 3.85 min; *m/z* 695 (MH^+).

Example 12: (2S)-3-(4-[[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid

To a solution of Intermediate 6 (0.172g) in dichloromethane (4ml), under a nitrogen atmosphere, was added Intermediate 56 (0.084g) and diisopropylethylamine (0.2ml). After stirring for 3h at 20°C the solution was diluted with dichloromethane (50ml) and washed with

saturated aqueous potassium carbonate (3 x 50ml), 1M hydrochloric acid (2 x 50ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (4:1) to give a white foam. To a solution of this in methanol (2ml) was added 1M sodium hydroxide (2ml) and the mixture was stirred for 1h at 20°C, then partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (50ml). The organic extract was washed with brine (50ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (4:1) to give the title compound as a white solid (0.041g, 23%). LCMS: R_t 3.72 min; *m/z* 705 (MH^+).

Example 13: (2S)-2-{((2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl)amino)-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl)oxy] phenyl}propanoic acid

To a solution of Intermediate 45 (0.055g) in acetonitrile (2ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.052g) and 1-hydroxybenzotriazole (0.038g). After stirring for 30 mins at 20°C Intermediate 8 (0.15g) was added followed by diisopropylethylamine (0.047ml), and stirring was continued for 18h. The mixture was diluted with chloroform (100ml) and washed with 1M hydrochloric acid (3 x 50ml), saturated aqueous sodium hydrogen carbonate (3 x 50ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white foam (0.189g). To a solution of this (0.176g) in methanol (4ml) was added 1M sodium hydroxide (1ml) and the mixture was stirred for 2h at 20°C, then partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (200ml). The organic extract was washed with brine (30ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with a gradient of chloroform/methanol (9:1) to chloroform/methanol (4:1) to give the title compound as a white solid (0.103g, 79%). LCMS: R_t 4.00 min; *m/z* 733 (MH^+).

Example 14: (2S)-2-{((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl)oxy] phenyl}propanoic acid

This was similarly prepared from Intermediate 43 (0.073g) and Intermediate 8 (0.15g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol (6:1) to give the title compound as a white solid (0.103g, 53%). LCMS: R_t 3.84 min; *m/z* 799 (MH^+).

Example 15: (2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{((2S)-2-{[2-(2-iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino}propanoic acid

To a solution of Intermediate 43 (0.07g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.05g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate 21 (0.135g) was added followed by diisopropylethylamine (0.05ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (2 x 50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with dichloromethane to give a white foam. To this was added trifluoroacetic acid (2ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.143g, 83%). LCMS: R_t 3.12 min; *m/z* 709 (MH^+).

Example 16: (2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid

To a solution of Intermediate 46 (0.052g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.05g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate 21 (0.135g) was added followed by diisopropylethylamine (0.05ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (2 x 50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with dichloromethane to give a white foam. To this was added trifluoroacetic acid (2ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.115g, 74%). LCMS: R_t 3.31 min; *m/z* 639 (MH^+).

Example 17: (2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino}propanoic acid

To a solution of (2-methylphenoxy)acetic acid (0.042g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.05g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate

21 (0.135g) was added followed by diisopropylethylamine (0.05ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (2 x 50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with dichloromethane to give a white foam. To this was added trifluoroacetic acid (2ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue triturated with ether to give the title compound as a white solid (0.124g, 86%). LCMS: R_t 3.10 min; *m/z* 597 (MH^+).

Example 18: (2S)-3-(4-[[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid

To a solution of Intermediate 45 (0.053g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.05g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate 21 (0.135g) was added followed by diisopropylethylamine (0.05ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (2 x 50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with dichloromethane to give a white foam. To this was added trifluoroacetic acid (2ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.127g, 83%). LCMS: R_t 3.33 min; *m/z* 643 (MH^+).

Example 19: (2S)-3-(4-[[(4-Benzoyl-1-piperazinyl)carbonyl]oxy)phenyl)-2-[((2S)-2-[[2-(2-iodophenoxy)acetyl]amino)-4-methylpentanoyl)amino]propanoic acid

This was similarly prepared from Intermediate 43 (0.07g) and Intermediate 22 (0.151g). The title compound was obtained as a white solid (0.152g, 81%).

LCMS: R_t 3.58 min; *m/z* 771 (MH^+).

Example 20: (2S)-3-(4-[[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-2-{[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino)propanoic acid

To a solution of Intermediate 46 (0.052g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.05g) and 1-hydroxybenzotriazole (0.04g). After stirring for 30 mins at 20°C Intermediate 22 (0.151g) was added followed by diisopropylethylamine (0.05ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (30ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (30ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (2 x 50ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was co-evaporated with dichloromethane to give a white foam. To this was added trifluoroacetic acid (2ml) and water (3 drops). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white foam (0.17g, 90%). LCMS: R_t 3.61 min; *m/z* 701 (MH^+).

Example 21: (2S)-3-(4-[[(4-Benzoyl-1-piperazinyl)carbonyl]oxy)phenyl)-2-{((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino]propanoic acid

To a solution of (2-methylphenoxy)acetic acid (0.472g) in acetonitrile (30ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.56g) and 1-hydroxybenzotriazole (0.4g). After stirring for 30 mins at 20°C a solution of Intermediate 22 (1.5g) in acetonitrile (25ml) was added and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (75ml). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (50ml), dried over sodium sulphate and evaporated *in vacuo* to give a white foam. To a solution of this in chloroform (12ml) was added trifluoroacetic acid (6ml). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was co-evaporated with chloroform and ether to give the title compound as a white foam (0.17g, 90%). LCMS: R_t 3.44 min; *m/z* 659 (MH^+).

Example 22: (2S)-3-(4-[[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-2-[[2-(2,4-dichlorophenoxy)acetyl]amino)-4-methylpentanoyl)amino]propanoic acid

This was similarly prepared from 2,4-dichlorophenoxyacetic acid (0.055g) and Intermediate 22 (0.151g). The title compound was obtained by trituration with ether as a white solid (0.129g, 75%). LCMS: R_t 3.52 min; *m/z* 713 (MH^+).

Example 23: (2S)-2-[((2S)-2-[[2-(2-Iodophenoxy)acetyl]amino]-4-methyl pentanoyl)amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To a solution of Intermediate 43 (0.556g) in acetonitrile (40ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.383g) and 1-hydroxybenzotriazole (0.27g). After stirring for 30 mins at 20°C Intermediate 23 (1g) was added followed by diisopropylethylamine (0.35ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (75ml). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (50ml), dried over sodium sulphate and evaporated *in vacuo* to give a white foam. To a solution of this in dichloromethane (20ml) was added trifluoroacetic acid (20ml) and water (1ml). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (1.15g, 92%). LCMS: R_t 3.68 min; *m/z* 668 (MH^+).

Example 24: (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To a solution of Intermediate 46 (0.416g) in acetonitrile (40ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.383g) and 1-hydroxybenzotriazole (0.27g). After stirring for 30 mins at 20°C Intermediate 23 (1g) was added followed by diisopropylethylamine (0.35ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (75ml). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (50ml), dried over sodium sulphate and evaporated *in vacuo* to give a white foam. To a solution of this in dichloromethane (20ml) was added trifluoroacetic acid (20ml) and water (1ml). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.63g, 53%). LCMS: R_t 3.90 min; *m/z* 598 (MH^+).

NMR (DMSO-d_6) δH 12.74 (br s, 1H), 8.38 (d, 1H), 7.81 (d, 1H), 7.20-7.25 (m's, 3H), 7.14 (m, 1H), 6.99 (d, 2H), 6.90 (m, 1H), 6.85 (d, 1H), 4.57 (d, 1H), 4.50 (m's, 3H), 3.61 (m, 4H), 3.52 (br m, 2H), 3.30-3.40 (excess 2H, obscured by water), 3.06 (dd, 1H), 2.90 (dd, 1H), 1.57 (m, 1H), 1.38-1.50 (m's, 2H), 1.35 (s, 9H), 0.87 (d, 3H), 0.85 (d, 3H).

Example 24 (Alternative Procedure): (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To Sasrin resin (125g) was added a solution of (2S)-3-[4-(allyloxy)phenyl]-2-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propanoic acid (300g) in DMF (970ml). After 15 mins pyridine (60ml) was added followed by 2,6-dichlorobenzoyl chloride (106.5ml) dropwise. The mixture was stirred for 18h at 20°C. The resin was filtered and washed with DMF (3 x 800ml), methanol (3 x 800ml) and dichloromethane (3 x 1l). The resin was treated with acetic anhydride (800ml) and pyridine (10ml) and the mixture was stirred for 3.5h at 45°C. After cooling to 20°C the resin was filtered and washed with NMP (3 x 800ml), methanol (3 x 800ml) and dichloromethane (3 x 800ml) then dried *in vacuo*.

200g of the resin was treated with 20% piperidine in DMF (1.2l) and stirred for 3h at 20°C. The resin was filtered and washed with DMF (3 x 1l), methanol (3 x 1l) and dichloromethane (3 x 1l). To this was added a solution of Fmoc-leucine (233.3g), 1,3-diisopropylcarbodiimide (84.7g) and 1-hydroxybenzotriazole (89.3g) in NMP (1.2l). The mixture was stirred for 18h at 20°C. The resin was filtered and washed with NMP (3 x 1l), methanol (3 x 1l) and dichloromethane (3 x 1l).

The resin was treated with 20% piperidine in DMF (1.2l) and stirred for 3h at 20°C. The resin was filtered and washed with DMF (3 x 1l), methanol (3 x 1l) and dichloromethane (3 x 1l). To this was added a solution of Intermediate 46 (68.8g), 1,3-diisopropylcarbodiimide (42.3g) and 1-hydroxybenzotriazole (44.7g) in NMP (1.2l). The mixture was stirred for 18h at 20°C. The resin was filtered and washed with NMP (3 x 1l), methanol (3 x 1l) and dichloromethane (3 x 1l).

To the resin was added dichloromethane (500ml), phenylsilane (160ml) and a slurry of tetrakis(triphenylphosphine)palladium(0) (34g) in dichloromethane (500ml). The mixture was stirred for 2h at 20°C. The resin was filtered and washed with dichloromethane (3 x 1l), ether (3 x 1l) and dichloromethane (6 x 1l).

A slurry of the resin in dichloromethane (800ml) was treated with diisopropylethylamine (120ml) followed by 4-nitrophenyl chloroformate (131g) in 3 portions at 10 minute intervals. The mixture was stirred for 2h at 20°C. The resin was filtered and washed with dichloromethane (3 x 1l), ether (3 x 1l) and DMF (3 x 1l). A slurry of the resin in DMF (800ml) was treated with a solution of morpholine (56.5ml) in DMF (200ml). The mixture was stirred for 2h at 20°C. The resin was filtered and washed with DMF (3 x 1l), ether (3 x 1l) and dichloromethane (3 x 1l).

A slurry of the resin in dichloromethane (400ml) was treated with 10% TFA in dichloromethane (800ml). After stirring for 30 mins at 20°C the resin was filtered and washed

with dichloromethane (2 x 500 ml). The combined filtrate and washings were evaporated *in vacuo*. The residue was triturated with ether (750ml) and the resulting white solid filtered. To this was added acetonitrile (500ml) and the mixture was heated to reflux. The hot solution was filtered and the filtrate allowed to cool to 20°C. The mixture was filtered to give the title compound as a white solid (50.9g).

Example 25: (2S)-2-[((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To a solution of (2-methylphenoxy)acetic acid (0.332g) in acetonitrile (40ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.383g) and 1-hydroxybenzotriazole (0.27g). After stirring for 30 mins at 20°C Intermediate 23 (1g) was added followed by diisopropylethylamine (0.35ml) and stirring was continued for 18h. The mixture was partitioned between 1M hydrochloric acid (50ml) and ethyl acetate (75ml). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (40ml) and water (50ml), dried over sodium sulphate and evaporated *in vacuo* to give a white foam. To a solution of this in dichloromethane (20ml) was added trifluoroacetic acid (20ml) and water (1ml). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.895g, 80%). LCMS: R_t 3.31 min; *m/z* 556 (MH^+).

Example 26: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl)oxy)phenyl]-2-[((2S)-2-[[2-(2-Iodophenoxy)acetyl]amino)-4-methylpentanoyl)amino]propanoic acid

This was similarly prepared from Intermediate 43 (0.06g) and Intermediate 24 (0.1g). The title compound was obtained as a white solid (0.07g, 56%).
LCMS: R_t 3.33 min; *m/z* 709 (MH^+).

Example 27: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl)oxy)phenyl]-2-[((2S)-4-methyl-2-[[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid

To a solution of (2-methylphenoxy)acetic acid (0.345g) in acetonitrile (50ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.4g) and 1-hydroxybenzotriazole (0.3g). After stirring for 30 mins at 20°C Intermediate 24 (1g) was added followed by diisopropylethylamine (0.35ml) and stirring was continued for 18h. The mixture was concentrated *in vacuo* and the residue was partitioned between 1M hydrochloric acid (100ml) and ethyl acetate (300ml). The layers were separated

and the organic phase was washed with 1M hydrochloric acid (2 x 100ml), saturated aqueous sodium hydrogen carbonate (3 x 100ml) and brine (100ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white solid. To a solution of this in chloroform (5ml) was added trifluoroacetic acid (5ml) and water (1ml). After stirring for 3h at 20°C the solvent was evaporated *in vacuo* and the residue was azeotroped with toluene (2 x 20ml) then triturated with ether to give the title compound as a white solid (1.06g, 98%). LCMS: R_t 3.20 min; *m/z* 597 (MH^+). Solubility in water: 0.01 mg/ml.
NMR (DMSO-d_6) δH 12.75 (br s, 1H), 8.33 (d, 1H), 7.81 (d, 1H), 7.32 (br s, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.11 (t, 1H), 6.98 (d, 2H), 6.79-6.89 (m's, 3H), 4.46-4.56 (AB system, 2H), 4.39-4.46 (m's, 2H), 3.95-4.14 (m's, 2H), 2.80-3.10 (m's, 4H), 2.33 (m, 1H), 2.20 (s, 3H), 1.75 (m, 2H), 1.40-1.60 (m's, 5H), 0.82-0.87 (m's, 6H).

Example 27 (Alternative Procedure): (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl) oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid

To Wang resin (50g) was added a solution of (2S)-3-[4-(allyloxy)phenyl]-2-[(tert-butoxycarbonyl)amino]propanoic acid (115.8g) and 1-hydroxybenzotriazole (48.6g) in DMF (475ml). After 15 minutes 1,3-diisopropylcarbodiimide (56.5ml) was added and the mixture was stirred for 24h at 45°C. The resin was filtered and washed with DMF (3 x 360ml), methanol (3 x 360ml) and dichloromethane (3 x 700ml). To a slurry of the resin in dichloromethane (644ml) was added pyridine (14.7ml). Acetic anhydride (26.9ml) was added and the mixture was stirred for 12h at 20°C. The resin was filtered and washed with dichloromethane (3 x 550ml), methanol (3 x 370ml) and dichloromethane (3 x 550ml).
A slurry of 20g of the resin in dichloromethane (100ml) was cooled to 2-5°C and treated with a solution of phenol (20g) in dichloromethane (80ml). Chlorotrimethylsilane (20ml) was added dropwise and the mixture was stirred for 6h at 2-5°C. The resin was filtered and washed with dichloromethane (3 x 200ml), methanol (3 x 200ml), 10% water in DMF (2 x 200ml), 10% diisopropylethylamine in DMF (3 x 200ml), DMF (200ml), methanol (3 x 200ml) and dichloromethane (3 x 200ml).
A slurry of the resin in DMF (55ml) was treated with a solution of Fmoc-leucine (32.7g) and 1-hydroxybenzotriazole (12.5g) in DMF (85ml). After 5 minutes 1,3-diisopropylcarbodiimide (19.3ml) was added and the mixture was stirred for 15h at 20°C. The resin was filtered and washed with DMF (3 x 150ml), methanol (3 x 150ml) and dichloromethane (3 x 150ml).
The resin was treated with 20% piperidine in DMF (180ml) and stirred for 1h at 20°C. The resin was filtered and washed with DMF (3 x 150ml), dichloromethane (3 x 150ml), DMF (3 x

150ml) and dichloromethane (3 x 150ml). To a slurry of this in DMF (50ml) was added a solution of (2-methylphenoxy)acetic acid (17.9g) and 1-hydroxybenzotriazole (14.6g) in DMF (100ml). After 5 minutes 1,3-diisopropylcarbodiimide (16.9ml) was added and the mixture was stirred for 65h at 20°C. The resin was filtered and washed with DMF (2 x 150ml), methanol (3 x 150ml) and dichloromethane (3 x 150ml).

A slurry of the resin in dichloromethane (60ml) was treated with a solution of tetrakis(triphenylphosphine)palladium(0) (5.21g) in dichloromethane (140ml) followed by morpholine (13ml). The mixture was stirred for 2h at 20°C then the resin was filtered and washed with dichloromethane (7 x 200ml).

A slurry of the resin in dichloromethane (160ml) was treated with diisopropylethylamine (12.4ml) followed by 4-nitrophenyl chloroformate (24.8g) in 3 portions at 5 minute intervals. The mixture was stirred for 1h at 20°C. The resin was filtered and washed with dichloromethane (3 x 200ml). The resin was treated with a solution of isonipecotamide (15.8g) in DMF (180ml) and the mixture was stirred for 1.5h at 20°C. The resin was filtered and washed with DMF (4 x 200ml) and dichloromethane (2 x 200ml).

The resin was treated with 50% TFA in dichloromethane (200ml). After stirring for 1h at 20°C the resin was filtered and washed with dichloromethane (5 x 200 ml). The combined filtrate and washings were evaporated *in vacuo*. The residue was azeotroped with toluene (2 x 100ml) then triturated with ether (50ml) and the resulting white solid filtered. To this was added acetonitrile (150ml) and the mixture was heated to reflux. The resulting suspension was allowed to cool to 20°C and stirred for 18h.. The mixture was filtered to give the title compound as a white solid (4.9g).

Example 27A: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid potassium salt

A suspension of Example 27 (10g) in methanol (150ml) was warmed to reflux to obtain a clear solution. To this was added a solution of potassium carbonate (1.16g) in water (7.5ml). After heating under reflux for two minutes the solvents were evaporated *in vacuo* to give a crisp foam. To this was added acetonitrile (100ml) and the mixture was warmed to reflux, during which time the foam collapsed and started to crystallise. After ten minutes the mixture was allowed to cool to 20°C then filtered under reduced pressure, washed with acetonitrile (25ml) and ether (50ml) to give the title compound as a white solid (10.65g, 100%). The product is believed to be isolated in the form of its monohydrate. Solubility in water: >250 mg/ml.

NMR (DMSO-d_6) δH 8.27 (d, 1H), 7.42 (d, 1H), 7.37 (d, 1H), 7.04-7.16 (m's, 4H), 6.78-6.88 (m's, 5H), 4.44-4.59 (AB system, 2H), 4.21 (m, 1H), 3.95-4.12 (br m's, 2H), 3.87 (m, 1H), 2.80-3.10 (m's, 4H), 2.34 (m, 1H), 2.20 (s, 3H), 1.75 (m, 2H), 1.41-1.60 (m's 5H), 0.86 (d, 3H), 0.80 (d, 3H).

Example 28: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-{{(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino) propanoic acid

To a solution of Intermediate 45 (0.438g) in acetonitrile (50ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.4g) and 1-hydroxybenzotriazole (0.29g). After stirring for 30 mins at 20°C Intermediate 24 (1g) was added followed by diisopropylethylamine (0.35ml) and stirring was continued for 18h. The mixture was concentrated *in vacuo* and the residue was partitioned between 1M hydrochloric acid (100ml) and ethyl acetate (300ml). The layers were separated and the organic phase was washed with 1M hydrochloric acid (2 x 100ml), saturated aqueous sodium hydrogen carbonate (3 x 100ml) and brine (100ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white solid. To a solution of this in chloroform (5ml) was added trifluoroacetic acid (5ml) and water (1ml). After stirring for 3h at 20°C the solvent was evaporated *in vacuo* and the residue was azeotroped with toluene (2 x 20ml) then triturated with ether to give the title compound as a white solid (0.95g, 80%). LCMS: R_t 3.48 min; *m/z* 643 (MH^+).

Example 29: (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid

To a solution of Intermediate 46 (0.1g) in acetonitrile (5ml), under a nitrogen atmosphere, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.09g) and 1-hydroxybenzotriazole (0.063g). After stirring for 30 mins at 20°C Intermediate 20 (0.18g) was added and stirring was continued for 18h. The mixture was partitioned between water (20ml) and ethyl acetate (20ml). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 x 30ml), water (30ml) and brine (30ml), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (20:1) to give a clear oil. To a solution of this in dichloromethane (8ml) was added trifluoroacetic acid (2ml). After stirring for 2h at 20°C the solvent was evaporated *in vacuo* and the crude product purified by flash column chromatography on silica gel eluting with

dichloromethane/methanol/acetic acid/water (240:15:3:2) to give the title compound as a white foam (0.08g, 36%). LCMS: R_t 4.07 min; *m/z* 707 (MH^+).

Example 30: (2S)-2-[((2S)-4-Methyl-2-[[2-(2-methylphenoxy)acetyl]amino) pentanoyl)amino]-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid

This was similarly prepared from (2-methylphenoxy)acetic acid (0.09g) and Intermediate 20 (0.3g). The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/acetic acid/water (240:15:3:2) to give the title compound as a white foam (0.116g, 34%). LCMS: R_t 3.56 min; *m/z* 665 (MH^+).

Example 31: (2S)-2-{((2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid

This was similarly prepared from Intermediate 45 (0.1g) and Intermediate 20 (0.176g). The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/acetic acid/water (180:15:3:2) to give the title compound as a white foam (0.075g, 35%). LCMS: R_t 4.09 min; *m/z* 711 (MH^+).

Example 32: (2S)-2-[[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino)-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl} oxy)phenyl]propanoic acid

This was similarly prepared from Intermediate 50 (0.124g) and Intermediate 20 (0.168g). The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/acetic acid/water (200:15:3:2) to give the title compound as a white foam (0.055g, 24%). LCMS: R_t 4.19 min; *m/z* 779 (MH^+).

Example 33: (2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino) propanoic acid

To a solution of Intermediate 26 (0.47g) in dichloromethane (8ml), under a nitrogen atmosphere, was added isonipecotamide (0.106g) and diisopropylethylamine (0.2ml). The mixture was stirred for 18h at 20°C then diluted with chloroform (100ml), washed with saturated aqueous potassium carbonate (3 x 50ml), 1M hydrochloric acid (3 x 50ml) and water (50ml), dried over magnesium sulphate and evaporated *in vacuo* to give a white foam. To a solution of this in chloroform (3ml) was added trifluoroacetic acid (3ml). After stirring for

4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.223g, 52%).
LCMS: R_t 3.35 min; *m/z* 639 (MH^+).

Example 34: (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino)-3-(4-{[([4-[(4-fluorobenzyl)amino]carbonyl}-1-piperidinyl) carbonyl]oxy}phenyl)propanoic acid

This was similarly prepared from Intermediate 26 (0.312g) and Intermediate 54 (0.181g). The title compound was obtained as a white solid (0.187g, 57%).
LCMS: R_t 3.71 min; *m/z* 747 (MH^+).

Example 35: (2S)-2-[((2S)-2-{[2-(2,4-Dichlorophenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl]propanoic acid

To a suspension of anhydrous potassium carbonate (0.057g) and sodium iodide (0.051g) in anhydrous DMF (1ml) was added 2,4-dichlorophenol (0.166g) followed by Intermediate 27 (0.2g). The mixture was stirred for 18h at 20°C then partitioned between saturated aqueous sodium hydrogen carbonate (10ml) and ethyl acetate (10ml). The layers were separated and the organic phase was further washed with saturated aqueous sodium hydrogen carbonate (10ml) and brine (10ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give a white foam. To a solution of this in dichloromethane (2ml) was added trifluoroacetic acid (2ml). After stirring for 2h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.146g, 70%). LCMS: R_t 3.70 min; *m/z* 610 (MH^+).

Example 36: (2S)-2-[((2S)-2-{[2-(2-Benzoylphenoxy)acetyl]amino)-4-methyl pentanoyl)amino]-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

This was similarly prepared from 2-hydroxybenzophenone (0.2g) and Intermediate 27 (0.2g). The title compound was obtained as a pale yellow foam (0.057g, 26%). LCMS: R_t 3.60 min; *m/z* 646 (MH^+).

Example 37: (2S)-2-[((2S)-4-Methyl-2-{[2-(2-propylphenoxy)acetyl]amino) pentanoyl)amino]-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

This was similarly prepared from 2-propylphenol (0.14ml) and Intermediate 27 (0.2g). The title compound was obtained as a white solid (0.141g, 70%).

LCMS: R_t 3.71 min; *m/z* 584 (MH^+).

Example 38: (2S)-2-{[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

This was similarly prepared from 1-bromo-2-naphthol (0.23g) and Intermediate 27 (0.2g). The title compound was obtained as a white solid (0.11g, 48%).
LCMS: R_t 3.91 min; *m/z* 670 (MH^+).

Example 39: (2S)-2-[((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To a suspension of anhydrous potassium carbonate (0.1g) and sodium iodide (0.06g) in anhydrous DMF (1ml) was added 2-cyclohexylphenol (0.12g) followed by Intermediate 27 (0.2g). The mixture was stirred for 18h at 20°C then partitioned between saturated aqueous sodium hydrogen carbonate (10ml) and ethyl acetate (10ml). The layers were separated and the organic phase was further washed with saturated aqueous sodium hydrogen carbonate (10ml) and brine (10ml), dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give a white foam. To a solution of this in dichloromethane (3ml) was added trifluoroacetic acid (3ml). After stirring for 2h at 20°C the solvent was evaporated *in vacuo* and the residue was azeotroped with toluene then triturated with ether to give the title compound as a white solid (0.118g, 55%). LCMS: R_t 4.16 min; *m/z* 624 (MH^+).

Example 40: (2S)-2-[((2S)-2-{[(Benzyloxy)carbonyl]amino}-4-methylpentanoyl) amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid

To a solution of Intermediate 13 (0.19g) in chloroform (2ml) was added trifluoroacetic acid (2ml). After stirring for 4h at 20°C the solvent was evaporated *in vacuo* and the residue was triturated with ether to give the title compound as a white solid (0.156g, 90%). LCMS: R_t 3.22 min; *m/z* 542 (MH^+).

Example 41: (2S)-3-[4-({[4-(2-Furoyl)-1-piperazinyl]carbonyl}oxy)phenyl]-2-{((2S) -2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino}propanoic acid

Intermediate 38 (0.26mmol) was treated with DMF (4ml). 2-Iodophenol (0.57g), potassium carbonate (0.36g) and sodium iodide (0.39g) were added and the mixture was shaken for 16h at 20°C. The resin was filtered and washed with water (2 x 5ml), DMF (5 x 5ml) and dichloromethane (5 x 5ml) then treated with 1:1 trifluoroacetic acid/ dichloromethane (4ml). After 30 mins the resin was filtered and the filtrate was evaporated *in vacuo*. The residue was azeotroped with toluene (5ml) then triturated with ether. The crude product was crystallised from acetonitrile to give the title compound as a white solid (0.043g).
LCMS: R_t 3.50 min; *m/z* 761 (MH^+).

Example 42: (2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-[4-(([4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid

Intermediate 38 (0.26mmol) was treated with DMF (4ml). 2-*tert*-butyl phenol (0.4ml), potassium carbonate (0.36g) and sodium iodide (0.39g) were added and the mixture was shaken for 16h at 20°C. The resin was filtered and washed with water (2 x 5ml), DMF (5 x 5ml) and dichloromethane (5 x 5ml) then treated with 1:1 trifluoroacetic acid/ dichloromethane (4ml). After 30 mins the resin was filtered and the filtrate was evaporated *in vacuo*. The residue was azeotroped with toluene (5ml) then triturated with ether. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:1) to give the title compound as a white solid (0.04g).
LCMS: R_t 3.63 min; *m/z* 691 (MH^+).

Example 43: (2S)-2-[((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-[4-(([4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid

This was similarly prepared from Intermediate 38 (0.26mmol) and 2-cyclohexyl phenol (0.46g). The crude product was purified using a solid phase extraction cartridge containing reverse phase silica eluting with a chloroform/methanol gradient (increasing from 98:2 to 80:20) to give the title compound as a cream solid (0.037g). LCMS: R_t 3.83 min; *m/z* 717 (MH^+).

Example 44: (2S)-2-{[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino}-3-[4-(([4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid

This was similarly prepared from Intermediate 38 (0.26mmol) and 1-bromo-2-naphthol (0.58g). The crude product was crystallised from acetonitrile to give the title compound as a cream coloured solid (0.064g). LCMS: R_t 3.69 min; *m/z* 763 (MH^+).

Example 45: (2S)-3-(4-[[(4-[[2-(4-Chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy)phenyl)-2-[((2S)-2-[[2-(2-cyclohexylphenoxy)acetyl]amino)-4-methylpentanoyl)amino]propanoic acid

This was similarly prepared from Intermediate 39 (0.29mmol) and 2-cyclohexyl phenol (0.48g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.073g). LCMS: R_t 4.13 min; *m/z* 789 (MH^+).

Example 46: (2S)-2-[((2S)-2-[[2-(2-Benzoylphenoxy)acetyl]amino)-4-methyl pentanoyl)amino]-3-(4-[[(4-[[2-(4-chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy)phenyl)propanoic acid

This was similarly prepared from Intermediate 39 (0.29mmol) and 2-hydroxybenzophenone (0.55g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.065g). LCMS: R_t 3.75 min; *m/z* 811 (MH^+).

Example 47: (2S)-3-(4-[[(4-[[2-(4-Chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy)phenyl)-2-[((2S)-2-[[2-(2-iodophenoxy)acetyl]amino)-4-methyl pentanoyl)amino]propanoic acid

Intermediate 37 (0.27mmol) was treated with 20% piperidine in DMF (5ml) and shaken for 1h at 20°C. The resin was filtered and washed with DMF (5 x 5ml). A solution of Intermediate 43 (0.154g) in DMF (3ml) was added followed by a solution of benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluoro phosphate (0.285g) in DMF (2ml) and diisopropylethylamine (0.26ml). The mixture was shaken for 18h at 20°C. The resin was filtered and washed with DMF (5 x 5ml) and dichloromethane (5 x 5ml), then treated with 1:1 trifluoroacetic acid/ dichloromethane (5ml). After 30 mins the resin was filtered and the filtrate was evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.083g). LCMS: R_t 3.76 min; *m/z* 833 (MH^+).

Example 48: (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino)-3-(4-[[(4-[[2-(4-chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy)phenyl)propanoic acid

This was similarly prepared from Intermediate 37 (0.27mmol) and Intermediate 46 (0.115g). The crude product was purified by flash column chromatography on silica gel eluting with

chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.107g). LCMS: R_t 3.93 min; *m/z* 763 (MH^+).

Example 49: (2S)-3-(4-[[(4-[[2-(4-Chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy)phenyl)-2-({((2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl)amino)propanoic acid

This was similarly prepared from Intermediate 37 (0.27mmol) and Intermediate 45 (0.117g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.056g). LCMS: R_t 3.80 min; *m/z* 765 $[M-H]^-$.

Example 50: (2S)-3-(4-[[(4-[[2-(4-Chlorophenyl)acetyl]amino)-1-piperidinyl) carbonyl]oxy}phenyl)-2-({((2S)-4-methyl-2-[(2-[[3-(1-piperidinylcarbonyl)-2-naphthyl]oxy}acetyl)amino]pentanoyl)amino)propanoic acid

This was similarly prepared from Intermediate 37 (0.27mmol) and Intermediate 44 (0.173g). The crude product was purified by flash column chromatography on silica gel eluting with chloroform/methanol/acetic acid (95:5:0.5) to give the title compound as a white solid (0.062g). LCMS: R_t 3.71 min; *m/z* 868 (MH^+).

Example 51: (2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino)-3-(4-[{((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy] phenyl}propanoic acid

Intermediate 33 (0.23mmol) was treated with 1:1 dichloromethane/THF (3ml). Intermediate 59 (0.105g) was added followed by diisopropylethylamine (0.16ml). After shaking for 18h at 20°C the resin was filtered, washed with dichloromethane (4 x 5ml) and ether (3 x 5ml) and then dried *in vacuo*. LCMS showed that some of the 4-nitrophenyl carbonate had been hydrolysed to the phenol so the resin was treated with 1:1 dichloromethane/THF (3ml), diisopropylethylamine (0.2ml) and 4-nitrophenyl chloroformate (0.23g). After shaking for 18h at 20°C the resin was filtered and washed with dichloromethane (4 x 5ml) then treated with 1:1 dichloromethane/THF (3ml). Intermediate 59 (0.07g) and diisopropylethylamine (0.12ml). After shaking for 18h at 20°C the resin was filtered and washed with dichloromethane (4 x 5ml) then treated with 1:1 trifluoroacetic acid/dichloromethane (3ml). After 30 mins the resin was filtered and the filtrate was evaporated *in vacuo*. The residue was co-evaporated with dichloromethane followed by ether to give the title compound as an off-white solid (0.083g). LCMS: R_t 3.99 min; *m/z* 729 (MH^+).

Example 52: (2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2-cyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid

This was similarly prepared from Intermediate 33 (0.23mmol) and Intermediate 57 (0.106g). The title compound was obtained as an off-white solid (0.073g).
LCMS: R_t 4.27 min; *m/z* 735 (MH^+).

Example 53: (2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2,2-dicyclohexylacetyl)amino]-1-piperidinyl} carbonyl)oxy]phenyl}propanoic acid

This was similarly prepared from Intermediate 33 (0.25mmol) and Intermediate 58 (0.144g). The title compound was obtained as an off-white solid (0.105g).
LCMS: R_t 4.63 min; *m/z* 817 (MH^+).

Example 54: (2S)-2-{[((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino]-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid

This was similarly prepared from Intermediate 34 (0.3mmol) and Intermediate 59 (0.196g). The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/acetic acid/water (240:15:3:2) to give the title compound as a pale yellow foam (0.091g). LCMS: R_t 3.49 min; *m/z* 687 (MH^+).

Example 55: (2S)-2-{[((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid

Intermediate 42 (0.27mmol) was treated with a solution of Intermediate 59 (0.178g) in 1:1 dichloromethane/THF (2ml) followed by diisopropylethylamine (0.95ml). After shaking for 2h at 20°C the resin was filtered and washed with dichloromethane (5 x 5ml) then treated with 1:1 trifluoroacetic acid/dichloromethane (3ml). After 30 mins the resin was filtered and the filtrate was evaporated *in vacuo*. The residue was triturated with ether to give the title compound as an off-white solid (0.074g). LCMS: R_t 4.04 min; *m/z* 755 (MH^+).

Example 56: (2S)-3-{4-[({4-[(2-Cyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-{((2S)-2-{[2-(2-cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino}propanoic acid

This was similarly prepared from Intermediate 42 (0.27mmol) and Intermediate 57 (0.18g). The title compound was obtained as an off-white solid (0.102g).
LCMS: R_t 4.22 min; *m/z* 761 (MH^+).

Biological Data

The compounds of the Examples were tested in assay (1), the Jurkat adhesion assay, and the results obtained were as follows:

Example	pIC_{50}	SEM*	n*
1	7.88	0.18	6
2	8.03	0.24	4
3	7.38	0.12	4
4	7.78	0.08	4
5	8.11	0.03	4
6	8.25	0.06	4
7	8.58	0.03	4
8	7.37	0.15	4
9	7.58	0.10	5
10	8.08	0.05	9
11	8.08	0.12	10
12	7.96	0.06	8
13	7.59	0.11	4
14	7.78	0.07	4
15	8.57	0.04	8
16	8.49	0.10	8
17	8.59	0.09	8
18	8.43	0.38	5
19	8.12	0.08	5
20	7.83	0.03	6
21	8.41	0.07	9
22	7.65	0.17	4
23	8.35	0.02	10
24	8.22	0.08	10

Example	pIC_{50}	SEM*	n*
25	8.50	0.08	10
26	8.53	0.03	4
27	8.55	0.10	7
28	8.46	0.05	10
29	7.79	0.08	6
30	8.24	0.03	4
31	7.59	0.04	4
32	7.62	0.13	6
33	8.46	0.03	9
34	7.57	0.14	4
35	8.18	0.06	6
36	7.91	0.07	6
37	8.24	0.07	6
38	7.81	0.15	4
39	7.65	0.12	4
40	8.04	0.15	4
41	8.03	0.07	4
42	7.98	0.07	6
43	7.65	0.07	6
44	7.62	0.05	5
45	7.24	0.11	6
46	7.36	0.04	4
47	7.48	0.07	4
48	7.38	0.04	4
49	7.35	0.06	4
50	7.60	0.10	4
51	7.86	0.05	8
52	7.48	0.21	4
53	6.81	0.10	5
54	8.25	0.03	5
55	7.21	0.13	4
56	7.06	0.19	6

*SEM standard error of the mean of n experiments

The compounds of Examples 16, 17, 20, 21, 23, 24, 27 and 28 were tested in assay (2) the CD3/VCAM-1 Co-stimulation of T-cell proliferation assay, and the results were obtained as follows:

Example	pIC_{50}
16	7.4
17	7.5
20	6.9
21	6.9
23	6.9
24	7.1
27	7.5
28	6.8

The compounds of Examples 16, 17, 20, 21, 23, 24, 27 and 28 were also tested in assay (3) the Inhibition of lung eosinophil infiltration and hyper-reactivity in the guinea pig (intratracheal dose given 0.5 hours before and 6 hours after antigen challenge) and the results were as follows:

Example	Dose (μg/kg body weight)	% Inhibition	
		Eosinophil Accumulation	Hyper-reactivity
16	0.2	62	80
	2	78	95
17	0.2	68	58
	2	61	88
20	0.2	67	85
	2	79	100
21	0.2	49	82
	2	79	85
23	2	51	79
24	0.2	26	44
	2	77	85
27	0.2	58	88
	2	90	87
28	0.2	3	70

	2	62	47
Dexamethasone (Positive Control)	200	55	80

The compounds of Examples 16, 17, 20, 21, 23, 24, 27 and 28 were also tested in assay (4) the RPMI 8866/MAdCAM-1 adhesion assay and the results were as follows:

Example	pIC_{50}	SEM*	n*
16	6.8	0.09	3
17	6.8	0.08	3
20	6.7	0.16	2
21	6.7	0.08	3
23	7.2	0.27	3
24	6.6	0.05	3
27	7.5	0.2	3
28	6.9	0.1	3

*SEM standard error of the mean of n experiments

Abbreviations

WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
PyBop	benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate
DIC	1,3-diisopropylcarbodiimide
HOBT	1-hydroxybenzotriazole
Boc	tert butoxycarbonyl
Fmoc	9-fluorenylmethoxycarbonyl
Cbz	carbobenzyloxy
DIPEA	diisopropylethylamine
DCM	dichloromethane
DMF	dimethylformamide
THF	tetrahydrofuran
NMP	1-methyl-2-pyrrolidinone

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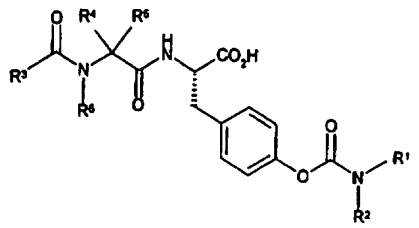
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

CLAIMS

1. A compound of formula I:



(I)

wherein R^1 and R^2 independently represent

(i) $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl or $-C_{1-3}$ alkylC_{3-6} cycloalkyl,

or such a group in which alkyl or cycloalkyl is substituted by one or more halogen, -CN, nitro, hydroxy or $-OC_{1-6}$alkyl groups;

(ii) $-(CH_2)_eAr^1$ or $-(CH_2)_eOAr^1$;

or NR^1R^2 together represent pyrrolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, morpholinyl or azepinyl, or such a group fused to a benzene ring, optionally substituted by one or more $-(CO)_n(CH_2)_rAr^1$, $-(CO)_nC_{1-6}$ alkylAr^1Ar^2, $-(CO)_nC_{1-6}$alkyl, $-(CH_2)_rOH$, $-(CH_2)_rO(CH_2)_pOH$, $-(CH_2)_rOC_{1-6}$ alkyl, $-O(CH_2)_rAr^1$, $-(CH_2)_rSO_2Ar^1$, piperidin-1-yl, $-(CH_2)_rCONR^8R^9$, $-NR^{10}(CO)_n(CH_2)_rAr^1$, $-NR^{10}(CO)_nC_{1-3}$alkylC_{3-6} cycloalkyl, $-NR^{10}(CO)_nC_{1-6}$ alkyldiC_{3-6} cycloalkyl, $-CONR^{10}(CH_2)_rAr^1$, halogen, $-NHSO_2C_{1-6}$alkyl, $-SO_2NR^{10}R^{11}$, $-SO_2C_{1-6}$ alkyl or $-SO_2Ar^2$ groups;

R^3 represents $-C_{1-6}$alkylNHC(=NH)NH_2, $-C_{2-6}$alkenylNHC(=NH)NH_2, $-C_{2-6}$alkynylNHC(=NH)NH_2, $-C_{1-6}$alkylN$R^{14}R^{15}$, $-(CH_2)_nCONR^{14}R^{15}$, $-(CH_2)_nCOC_{1-6}$alkyl, $-(CH_2)_qCHNR^{16}CONR^{20}R^{21}$, $-(CH_2)_mNR^{16}CONR^{14}R^{15}$, $-(CH_2)_qNR^{16}Ar^3$, $-(CH_2)_qCONR^{16}Ar^3$, $-(CH_2)_nCOOR^{16}$, $-(CH_2)_cAr^3$, $-O(CH_2)_cAr^3$, $-(CH_2)_qCO(CH_2)_tAr^3$ or $-(CH_2)_qOAr^3$;

or R^3 represents $-(CH_2)_c$-2,4-imidazolidinedione, $-(CH_2)_c$(piperidin-4-yl), $-(CH_2)_c$(piperidin-3-yl), $-(CH_2)_c$(piperidin-2-yl), $-(CH_2)_c$(morpholin-3-yl) or $-(CH_2)_c$(morpholin-2-yl) optionally substituted on nitrogen by $-(CO)_fC_{1-6}$alkyl, $-(CO)_f(CH_2)_cAr^2$ or $-C(=NH)NH_2$;

or R^3 represents $-(CH_2)_x$dibenzofuran optionally substituted by $-C_{1-6}$alkyl or halogen;

or R^3 represents $-(CH_2)_c$-thioxanthen-9-one;

R^4 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{1-3}$ alkylC_{3-6} cycloalkyl, $-(CH_2)_qAr^2$, $-C_{1-4}$alkyl-X-R^7, $-C_{1-6}$alkyl SO_2C_{1-4} alkyl, $-C_{1-6}$alkylN$R^{12}R^{13}$ or $-C_{1-6}$ alkylN$R^{12}COC_{1-6}$ alkyl;

R^5 represents hydrogen, or R^4R^5 together with the carbon to which they are attached form a C_{5-7} cycloalkyl ring;

R^6 represents hydrogen or $-C_{1-6}$alkyl, or R^6 and R^4 together with the N and C atoms to which they are respectively attached form a pyrrolidine ring;

R^7 represents hydrogen, $-(CH_2)_wNR^{12}R^{13}$, $-(CH_2)_cAr^2$ or $-(CH_2)_wNR^{12}COC_{1-6}$ alkyl;

R^8, R^9, R^{16} and R^{17} independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-C_{1-3}$ alkylC_{3-6} cycloalkyl, $-C_{2-6}$alkenyl or NR^8R^9 or $NR^{16}R^{17}$ together represents morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl or piperazinyl N-substituted by $-C_{1-6}$ alkyl, -COphenyl or $-SO_2$methyl;

R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, R^{18}, R^{20} and R^{21} independently represent hydrogen or $-C_{1-6}$alkyl;

R^{14}, R^{19} and R^{22} independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{3-6}$ cycloalkyl or $-(CH_2)_sAr^4$ or $NR^{14}R^{15}$ or $NR^{15}R^{22}$ together represents morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl;

Ar^1 represents phenyl or a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S optionally substituted by one or more halogen, C_{1-6}alkyl, hydroxy, $-OC_{1-6}$alkyl, CF_3, nitro, $-Ar^3$ or $-OAr^3$ groups;

Ar^2 represents phenyl optionally substituted by one or more halogen, $-C_{1-6}$alkyl, hydroxy, $-OC_{1-6}$alkyl, $-CF_3$ or nitro groups;

Ar^3 represents phenyl, a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N or S, or such a group fused to a benzene ring, optionally substituted by one or more $-CO(CH_2)_gAr^4$, $-(CH_2)_fAr^4$, $-(CH_2)_yCOAr^4$, $-(CO)_aC_{1-6}$ alkyl, $-(CO)_aC_{2-6}$ alkenyl, $-(CO)_aC_{2-6}$ alkynyl, $-(CO)_aC_{3-6}$cycloalkyl, $-(CO)_aC_{1-6}$haloalkyl, halogen, $-COCH_2CN$, $-(CH_2)_bNR^{16}R^{17}$, $-(CH_2)_bNHC(=NH)NH_2$, $-CYNR^{16}(CO)_aR^{17}$, $-(CH_2)_bNR^{15}COR^{19}$, $-(CH_2)_bCONR^{15}R^{22}$, $-(CH_2)_bNR^{15}CONR^{15}R^{22}$, $-(CH_2)_bCONR^{15}(CH_2)_jNR^{15}R^{22}$, $-(CH_2)_bSO_2NR^{15}R^{22}$, $-(CH_2)_bSO_2NR^{15}COAr^2$, $-(CH_2)_bNR^{15}SO_2R^{19}$, $-SO_2R^{19}$, $-SOR^{19}$, $-(CH_2)_zOH$, $-COOR^{15}$, -CHO, $-OC_{1-10}$alkyl, $-O(CH_2)_jNR^{15}R^{22}$, $-O(CH_2)_jNHC(=NH)NH_2$, $-O(CH_2)_bCONR^{16}R^{17}$, $-O(CH_2)_bCOOR^{15}$, $-O(CH_2)_jOAr^2$, $-O(CH_2)_bAr^2$, 3-phenyl-2-pyrazolin-5-one or 4,5-dihydro-3(2H)-pyridazinone groups;

Ar^4 represents phenyl or a 5 or 6 membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S optionally substituted by one or more halogen, $-C_{1-6}$alkyl, hydroxy, $-OC_{1-6}$alkyl, $-CF_3$, nitro or $-CONH_2$ groups;

X and Y independently represent O or S;

a, f, k, s and n independently represent 0 or 1;

b, c, r, x, y and z independently represent an integer 0 to 2;

d, g and u independently represent 1 or 2;

e, h, q and w independently represent an integer 1 to 3;

j and p independently represent an integer 2 to 4;

m independently represents an integer 0 to 4;

t independently represents an integer 0 to 3;

and salts and solvates thereof.

2. A compound according to claim 1 wherein R^4 represents $-C_{1-6}$ alkyl, R^5 represents hydrogen or R^4R^5, together with the carbon to which they are attached, forms a cyclohexyl ring, and R^6 represents hydrogen or methyl.

3. A compound according to claim 2 wherein R^4 represents $-C_{1-6}$ alkyl and R^5 and R^6 represent hydrogen.

4. A compound according to claim 3 wherein R^4 represents $-CH_2CHMe_2$ and R^5 and R^6 represent hydrogen.

5. A compound according to any one of claims 1 to 4 wherein NR^1R^2 together represents piperidinyl, piperazinyl, thiomorpholinyl, morpholinyl or 1,2,3,4-tetrahydroisoquinoline optionally substituted by a $-(CO)_n(CH_2)_rAr^1$, $-(CO)_nC_{1-6}$alkyl, $-(CH_2)_rCONR^8R^9$, $-NR^{10}(CO)_n(CH_2)_rAr^1$, $-NR^{10}(CO)_nC_{1-3}$ alkylC_{3-6} cycloalkyl, $-NR^{10}(CO)_nC_{1-6}$ alkyldiC_{3-6} cycloalkyl, $-(CH_2)_rOC_{1-6}$ alkyl, $-(CH_2)_rO(CH_2)_pOH$, piperidin-1-yl, $-(CH_2)_rOH$ or $-CONR^{10}(CH_2)_rAr^1$ group.

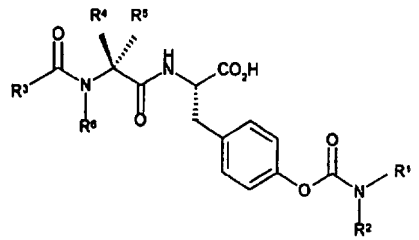
6. A compound according to claim 5 wherein NR^1R^2 together represents morpholinyl or piperazinyl optionally N-substituted by $-(CO)_nC_{1-6}$ alkyl, piperazinyl N-substituted by $-(CO)_n(CH_2)_rAr^1$, piperidinyl substituted by $-NR^{10}(CO)_n(CH_2)_rAr^1$ or piperidinyl substituted by $-(CH_2)_rCONR^8R^9$.

7. A compound according to any one of claims 1 to 6 wherein R^3 represents $-(CH_2)_c$-2,4-imidazolidinedione-3-yl, $-(CH_2)_c$-thioxanthen-9-one-3-yl, $-(CH_2)_cAr^3$, $-O(CH_2)_cAr^3$, $-(CH_2)_cOAr^3$ or $-(CH_2)_c$dibenzofuran.

8. A compound according to claim 7 wherein R^3 represents $-OCH_2Ar^3$, $-CH_2OAr^3$ or dibenzofuran.

9. A compound according to claim 8 wherein R^3 represents $-CH_2OAr^3$.

10. A compound according to any one of claims 1 to 9 wherein R^4 and R^5 have the stereochemical orientation shown in formula (Ia):



(Ia)

11. A compound of formula (I) which is:

(2S)-2-[((2S)-2-[[2-(2-Benzoylphenoxy)acetyl]amino]-4-methyl pentanoyl)amino]-3-{4-[((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid;

(2S)-2-({(2S)-4-Methyl-2-[(2-[[3-(1-piperidinylcarbonyl)-2-naphthyl] oxy)acetyl)amino]pentanoyl}amino)-3-{4-[((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl)oxy]phenyl}propanoic acid;

(2S)-3-{4-[((4-[(2,2-Dicyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-{((2S)-4-methyl-2-({2-[4-(1-piperidinylcarbonyl)phenoxy]acetyl} amino)pentanoyl]amino}propanoic acid;

(2S)-2-[[(2S)-4-Methyl-2-({2-[4-(1-piperidinylcarbonyl)phenoxy] acetyl}amino)pentanoyl]amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl} propanoic acid;

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-{((2S)-4-methyl-2-({2-[4-(1-piperidinylcarbonyl)phenoxy]acetyl}amino)pentanoyl] amino}propanoic acid;

(2S)-3-{4-[((4-[(2-Cyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-[((2S)-2-[[2-(2-Iodophenoxy)acetyl]amino}-4-methylpentanoyl) amino]propanoic acid;

(2S)-3-{4-[((4-[(2,2-Dicyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-[((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methylpentanoyl) amino]propanoic acid;

(2S)-2-({(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-({(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-{4-[((4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl)oxy] phenyl}propanoic acid;

(2S)-2-[((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[((4-[(2-phenylacetyl)amino}-1-piperidinyl}carbonyl)oxy] phenyl}propanoic acid;

(2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-2-[[2-(2-Iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-2-{[2-(2-iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-2-{[2-(2,4-dichlorophenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-2-[[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid;

(2S)-2-[((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino]-3-{4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid;

(2S)-2-{{(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid;

(2S)-2-{[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino}-3-[4-({[4-(1-piperidinylcarbonyl)-1-piperidinyl]carbonyl} oxy)phenyl]propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-(4-[[(4-{[(4-fluorobenzyl)amino]carbonyl}-1-piperidinyl) carbonyl]oxy}phenyl)propanoic acid;

(2S)-2-[((2S)-2-{[2-(2,4-Dichlorophenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{((2S)-2-{[2-(2-Benzoylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{((2S)-4-Methyl-2-{[2-(2-propylphenoxy)acetyl]amino} pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{((2S)-2-{[(Benzyloxy)carbonyl]amino}-4-methylpentanoyl) amino]-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-3-{4-({[4-(2-Furoyl)-1-piperazinyl]carbonyl}oxy)phenyl]-2-{((2S) -2-{[2-(2-iodophenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-2-{((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-2-{[(2S)-2-({2-[(1-Bromo-2-naphthyl)oxy]acetyl}amino)-4-methylpentanoyl]amino}-3-{4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-3-{4-[{(4-{[2-(4-Chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)-2-[((2S)-2-{[2-(2-cyclohexylphenoxy)acetyl]amino}-4-methylpentanoyl)amino]propanoic acid;

(2S)-2-{((2S)-2-{[2-(2-Benzoylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-(4-{[(4-{[2-(4-chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)propanoic acid;

(2S)-3-(4-{[(4-{[2-(4-Chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)-2-{((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methyl pentanoyl)amino]propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-(4-{[(4-{[2-(4-chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)propanoic acid;

(2S)-3-(4-{[(4-{[2-(4-Chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid;

(2S)-3-(4-{[(4-{[2-(4-Chlorophenyl)acetyl]amino}-1-piperidinyl) carbonyl]oxy}phenyl)-2-({(2S)-4-methyl-2-[(2-{[3-(1-piperidinylcarbonyl)-2-naphthyl]oxy}acetyl)amino]pentanoyl}amino)propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2-cyclohexylacetyl)amino]-1-piperidinyl} oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2,2-dicyclohexylacetyl)amino]-1-piperidinyl} carbonyl)oxy]phenyl}propanoic acid;

(2S)-2-[((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino]-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid;

(2S)-2-[((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}propanoic acid;

(2S)-3-{4-[({4-[(2-Cyclohexylacetyl)amino]-1-piperidinyl}carbonyl) oxy]phenyl}-2-{((2S)-2-{[2-(2-cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino]propanoic acid;

and salts and solvates thereof.

12. A compound of formula (I) which is:

(2S)-2-{((2S)-2-{[2-(2-Iodophenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid;

(2S)-2-{((2S)-2-{[2-(2-Cyclohexylphenoxy)acetyl]amino}-4-methyl pentanoyl)amino}-3-{4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-{4-[({4-[(2-phenylacetyl)amino]-1-piperidinyl}carbonyl) oxy] phenyl}propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid;

(2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid;

(2S)-2-{[(2S)-2-({2-[2-(Tert-butyl)phenoxy]acetyl}amino)-4-methyl pentanoyl]amino}-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-2-{{(2S)-2-[(Dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methyl pentanoyl}amino)-3-[4-({[4-(2-furoyl)-1-piperazinyl]carbonyl}oxy)phenyl] propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino]propanoic acid;

(2S)-3-(4-{[(4-Benzoyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-({(2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl}amino)propanoic acid;

and salts and solvates thereof.

13. A compound of formula (I) which is:
(2S)-3-(4-{[(4-Acetyl-1-piperazinyl)carbonyl]oxy}phenyl)-2-{((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino]propanoic acid;
(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-{((2S)-2-[(dibenzo[b,d]furan-4-ylcarbonyl)amino]-4-methylpentanoyl)amino) propanoic acid;
(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[[(2S)-2-({2-[2-(tert-butyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino) propanoic acid;
(2S)-2-{((2S)-4-Methyl-2-{[2-(2-methylphenoxy)acetyl]amino} pentanoyl)amino]-3-[4-[(4-morpholinylcarbonyl)oxy]phenyl}propanoic acid;
(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-2-{[2-(2-benzoylphenoxy)acetyl]amino}-4-methylpentanoyl)amino] propanoic acid;
(2S)-2-{[(2S)-2-({2-[4-(Aminocarbonyl)phenoxy]acetyl}amino)-4-methylpentanoyl]amino}-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy) phenyl]propanoic acid;
and salts and solvates thereof.

14. A compound of formula (I) which is:
(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino)pentanoyl)amino] propanoic acid or a salt or solvate thereof.

15. A compound of formula (I) according to claim 14 which is:
(2S)-3-[4-({[4-(Aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid potassium salt or a solvate thereof.

16. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

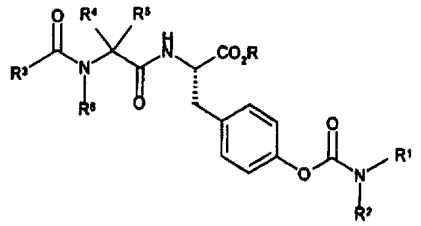
17. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15 or a physiologically acceptable salt or solvate thereof in combination together with a long acting β_2 adrenergic receptor agonist.

18. A compound of formula (I) as defined in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

19. Use of a compound of formula (I) as defined in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.

20. A method of treatment or prophylaxis of inflammatory diseases eg. asthma which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof.

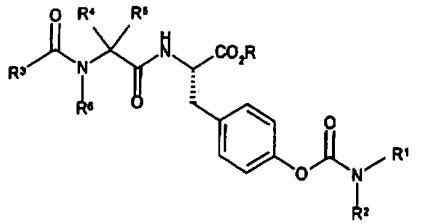
21. A process for preparation of a compound of formula (I) as defined in any one of claims 1 to 20 which comprises
(a) hydrolysis of a carboxylic acid ester of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claims 1 to 10 and R is a group capable of forming a carboxylic acid ester; or
(b) deprotecting a compound of formula (I) which is protected.

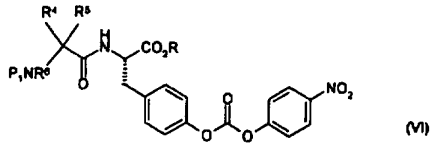
22. A compound of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claims 1 to 10 and R is a group capable of forming a carboxylic acid ester.

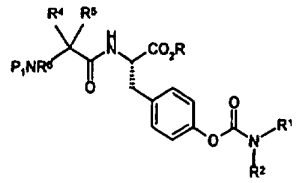
23. A compound of formula (VI)



(VI)

wherein P_1 represents Boc, R^4, R^5 and R^6 are as defined in claims 1 to 4 and 10, and R represents a group capable of forming a carboxylic acid ester.

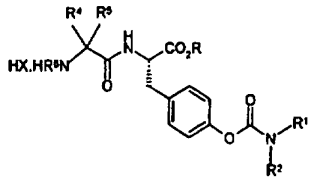
24. A compound of formula (VII)



(VII)

wherein P_1 represents Boc, R^1, R^2, R^4, R^5 and R^6 are as defined in claims 1 to 6 and 10, and R represents a group capable of forming a carboxylic acid ester.

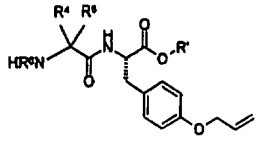
25. A compound of formula (VIII)



(VIII)

wherein R^1, R^2, R^4, R^5 and R^6 are as defined in claims 1 to 6 and 10, HX is a hydrohalic acid and R represents a group capable of forming a carboxylic acid ester.

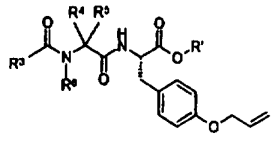
26. A compound of formula (XIII)



(XIII)

wherein R^4, R^5 and R^6 are as defined in claims 1 to 4 and 10 and R' represents a hydroxy functionalised polystyrene resin.

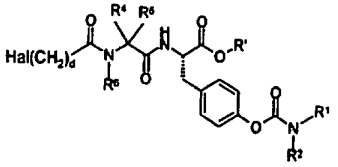
27. A compound of formula (XIV)



(XIV)

wherein R^3, R^4, R^5 and R^6 are as defined in claims 1 to 4 and 7 to 10 and R' represents a hydroxy functionalised polystyrene resin.

28. A compound of formula (XXI)



(XXI)

wherein R^1, R^2, R^4, R^5, R^6 and d are as defined in claims 1 to 6 and 10, R' represents a hydroxy functionalised polystyrene resin and Hal represents halogen.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 99/10000

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D295/20 C07D307/91 C07D405/12 C07D307/66
C07C271/40 C07K5/06 C07K17/08 C07K1/04 A61K31/325
A61K31/445 A61K31/496 A61K31/5375 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 53817 A (MERK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application schemes 1-5 claims 1,11,13; examples	1,16, 18-21, 26-28
A	WO 98 53814 A (MERCK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application scheme 1 claims 1,5,154,18-20; examples	1,16, 18-21, 26-28
A	WO 98 53818 A (MERCK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application claims 1,5,8-10	1,16, 18-20

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2000	29/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 99/10000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 201 121 A (FARBWERKE HOECHST AG) 5 August 1970 (1970-08-05) claims 1,4,5,7; examples	1,16, 22-25
A	US 4 105 602 A (R. L. COLESCOTT ET AL.) 8 August 1978 (1978-08-08) column 2, line 26 - line 37 columns 3 and 4, bottom of page, coupling reaction; columns 5 and 6, top of page, coupling reaction	26-28
A	WO 98 54207 A (CELLTECH THERAPEUTICS LTD.) 3 December 1998 (1998-12-03) cited in the application	
A	WO 97 03094 A (BIOGEN, INC.) 30 January 1997 (1997-01-30) cited in the application	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/10000

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/10000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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